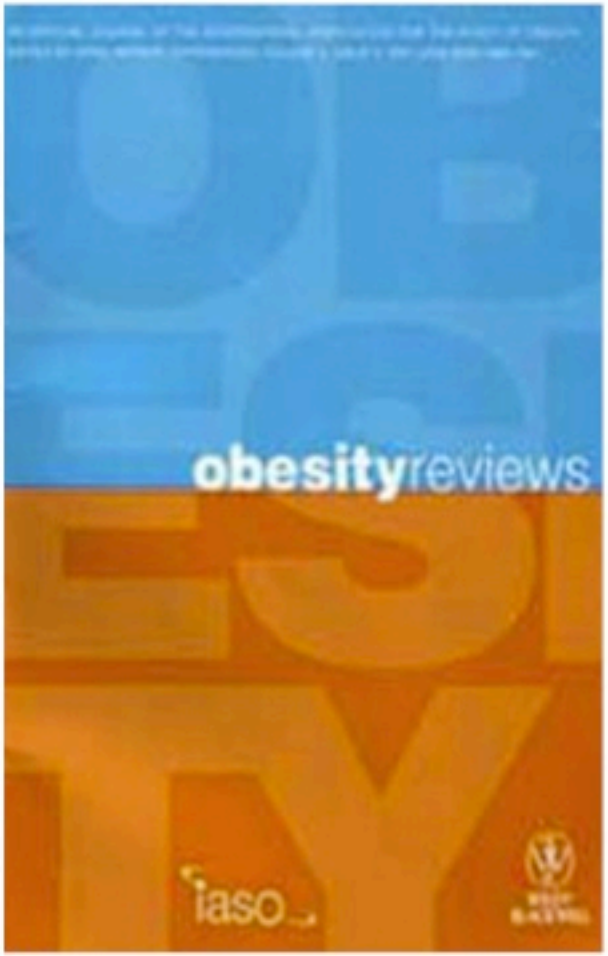
Farmaci anti-obesità: essere o non essere?



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

Dvorak RV, Sharma AM, Astrup A.

Obes Rev. 2010 Dec;11(12):833-4.

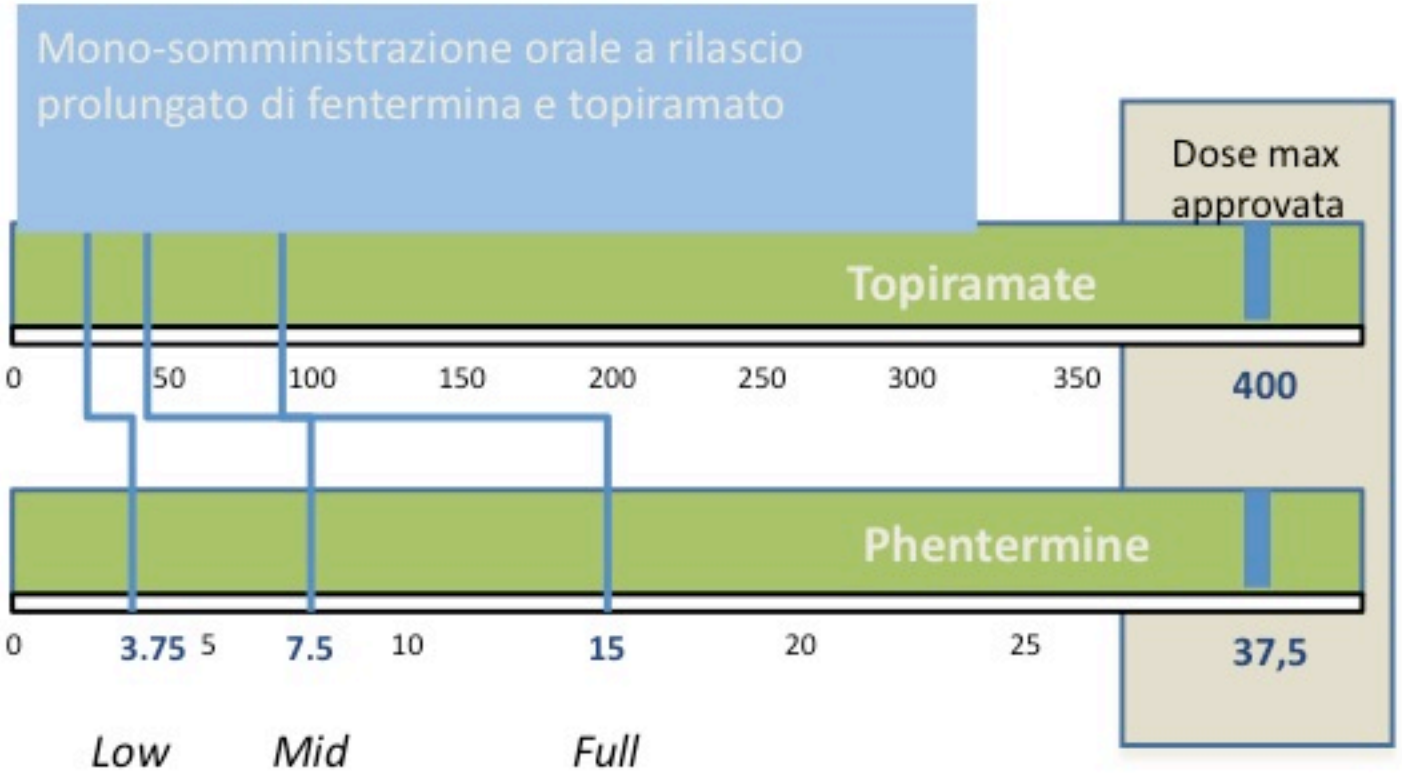
Dopo questo articolo vi è stato un ampio dibattito negli Usa sull'uso dei farmaci antiobesità

Approvato FDA nel luglio 2012

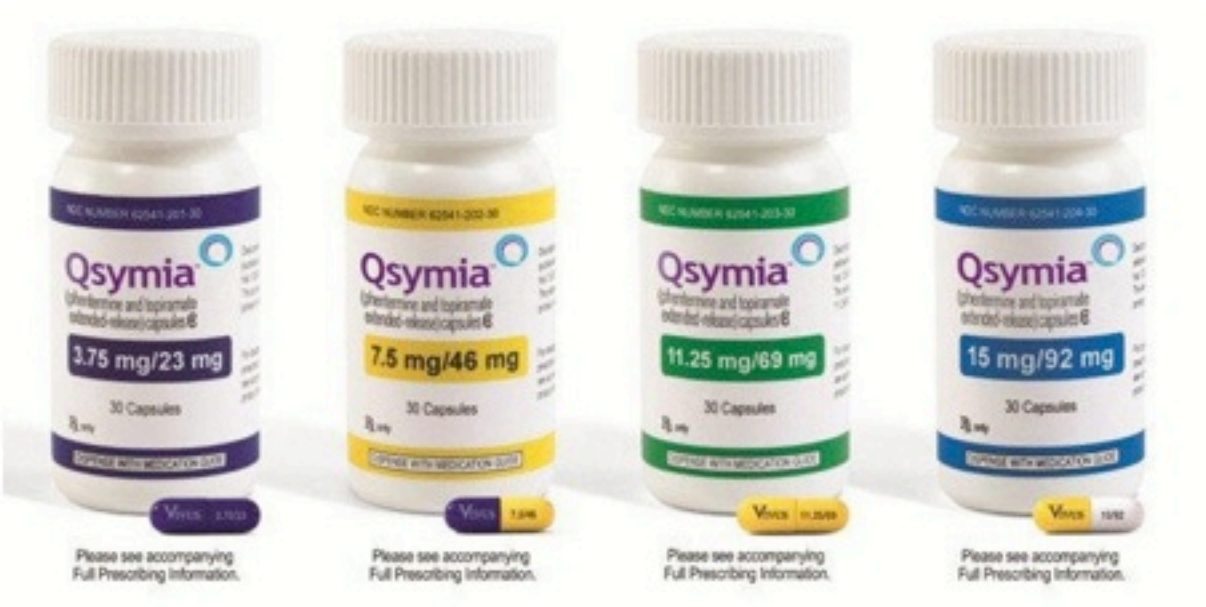
Fentermina + Topiramato (Qnexa) >>> (Qysmia)

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



In commercio negli USA: approvate 4 formulazioni

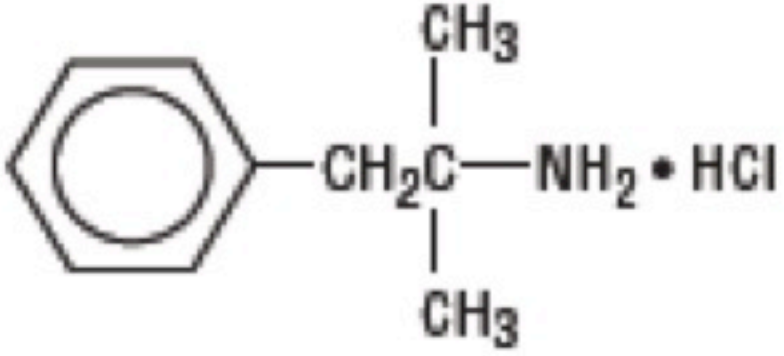


FENTERMINA –TOPIRAMATO : 3,75/23 -----7,5/46------11,25/69----15/92

ADIPEX-P® ℂ
(Phentermine Hydrochloride USP, 37.5 mg)
℞ only

DESCRIPTION

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



$C_{10}H_{15}N \cdot HCl$ M.W. 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)

DOSAGE 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 3)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- 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.

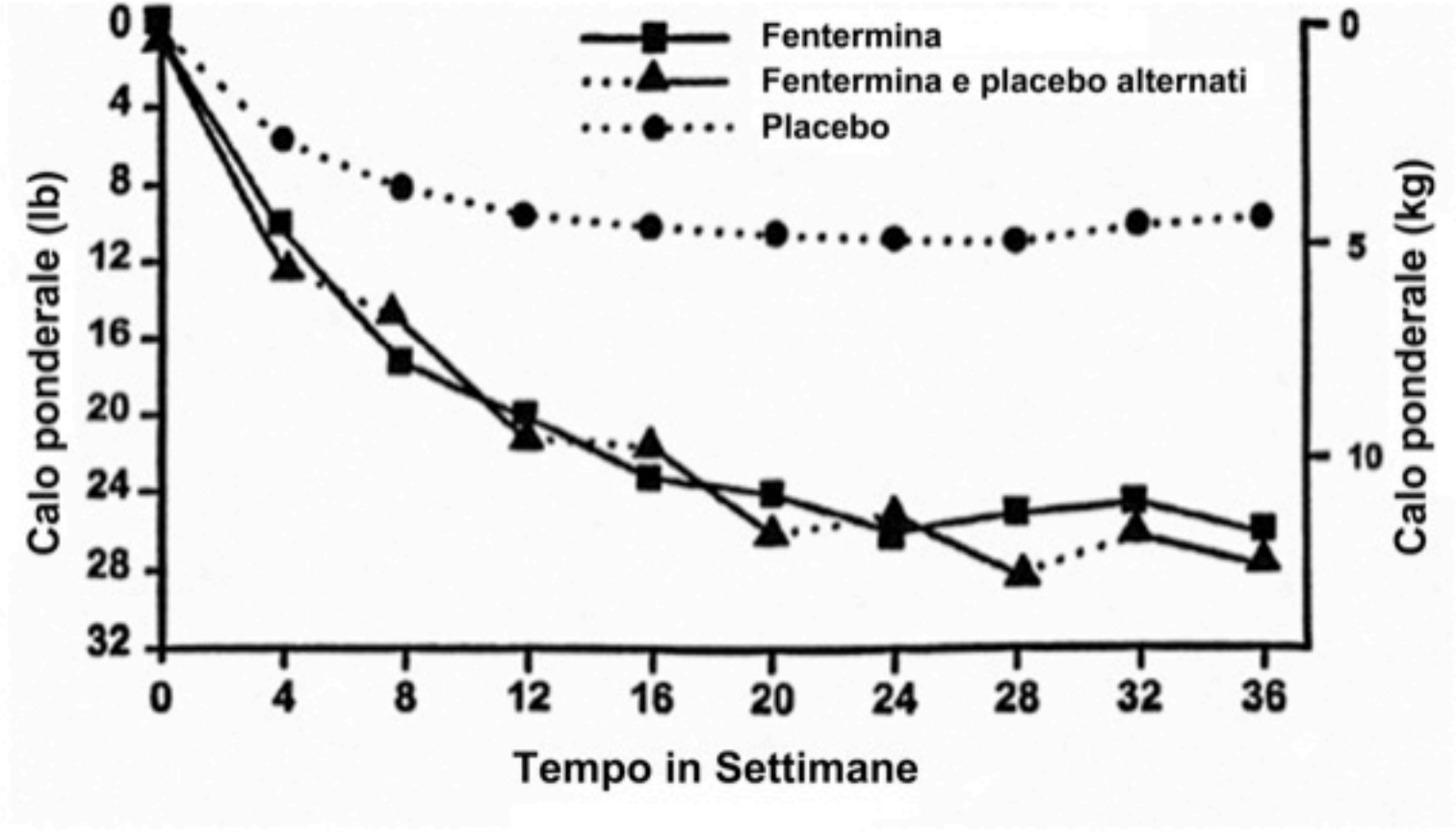
Controindicazioni

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.

Sia il trattamento continuativo che quello intermittente con fentermina hanno portato a una maggiore perdita di peso rispetto al placebo

(tratto e adattato da Munro JF, MacCuish AC, Wilson EM et al. Br Med J. 1968 Feb 10;1:352-4).



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)

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

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)

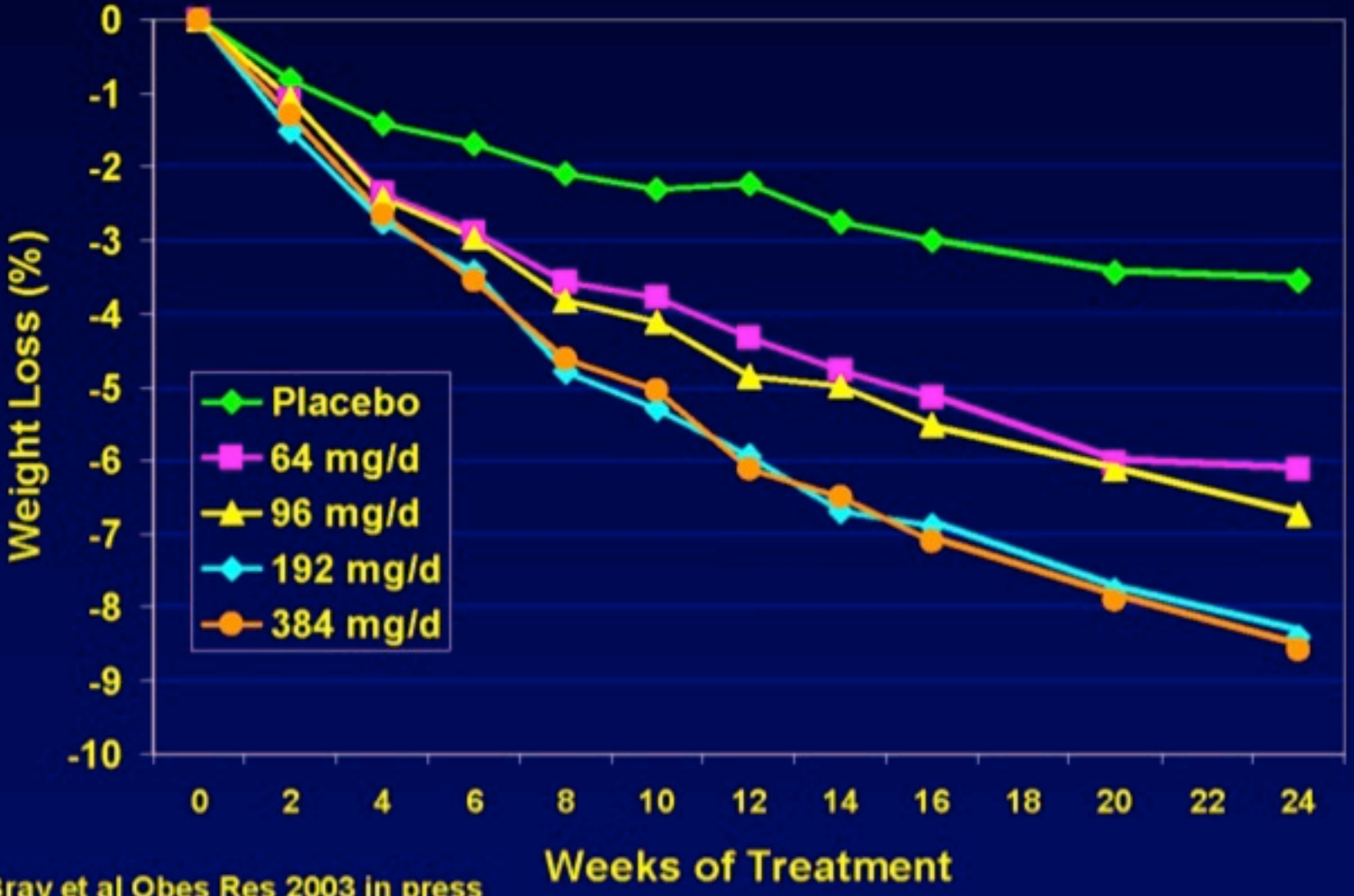
Hyperammonemia and encephalopathy associated with or without concomitant valproic acid use: Patients with inborn errors of metabolism or reduced mitochondrial activity may have an increased risk of hyperammonemia Measure ammonia if encephalopathic symptoms occur (5 9)

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

Eventi avversi Topiramato

Table 3 Meta-analysis of adverse events

Adverse event	No. of reports describing the event	No. of participants reporting the even/total no. of participants		Pooled OR	95%CI	I^2	*P* value (heterogeneity)
		Intervention group	Control group				
Any event leading to topiramate withdrawal	12	446/2628	245/2525	1.94	1.64–2.29	0	0.87
Paraesthesia	17	1442/3035	289/3027	8.70	6.90–11.0	58.5	<0.001
Taste perversion	16	277/2981	30/2970	8.61	5.35–13.87	25.9	0.16
Psychomotor impairment	7	61/1264	6/1266	7.82	3.71–16.46	0	0.98
Hypoesthesia	9	109/1146	20/1133	4.51	2.76–7.40	0	0.52
Anorexia	11	215/2056	69/2034	3.33	2.51–4.41	0	0.99
Concentration difficulty	16	292/2981	91/2970	3.30	2.55–4.27	4.5	0.40
Nervousness	7	74/1265	26/1266	2.93	1.89–4.63	0	0.97
Visual disturb	5	88/1315	37/1326	2.48	1.66–3.70	0	0.69
Dry month	12	193/2676	88/2670	2.21	1.62–3.02	20.1	0.25
Memory impairment	15	276/2603	142/2611	2.05	1.63–2.58	8.9	0.35
Mood problems	11	116/1942	59/1992	2.00	1.44–2.77	0	0.82
Cough	9	139/1697	86/1682	1.58	1.20–2.11	0	0.47
Depression	15	213/2778	141/2770	1.55	1.24–1.94	0	0.83
Nausea	9	161/1716	109/1704	1.52	1.17–1.96	0	0.90
Constipation	12	156/2106	92/2099	1.71	1.31–2.25	0	0.60
Dyspepsia	7	50/791	29/773	1.71	1.06–2.76	0	0.91
Abdominal pain	9	129/1618	92/1618	1.37	0.98–1.92	14.9	0.31
Dizziness	14	291/2477	221/2465	1.35	1.11–1.63	2.4	0.42
Fatigue	16	529/2843	413/2825	1.34	1.16–1.55	0.3	0.45
Back pain	6	77/737	58/716	1.32	0.92–1.90	0	0.84
Insomnia	12	120/2091	90/2091	1.31	0.98–1.74	0	0.63
Somnolence	11	136/1874	107/1877	1.27	0.98–1.67	0	0.61
Upper respiratory tract infection	11	716/2375	609/2367	1.26	1.10–1.43	0	0.66
Diarrhea	11	214/2071	171/2056	1.26	1.02–1.56	0	0.70
Migraine	7	127/1342	113/1330	1.11	0.84–1.47	0	0.52

CI, confidence interval; No., number; OR, odds ration.

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

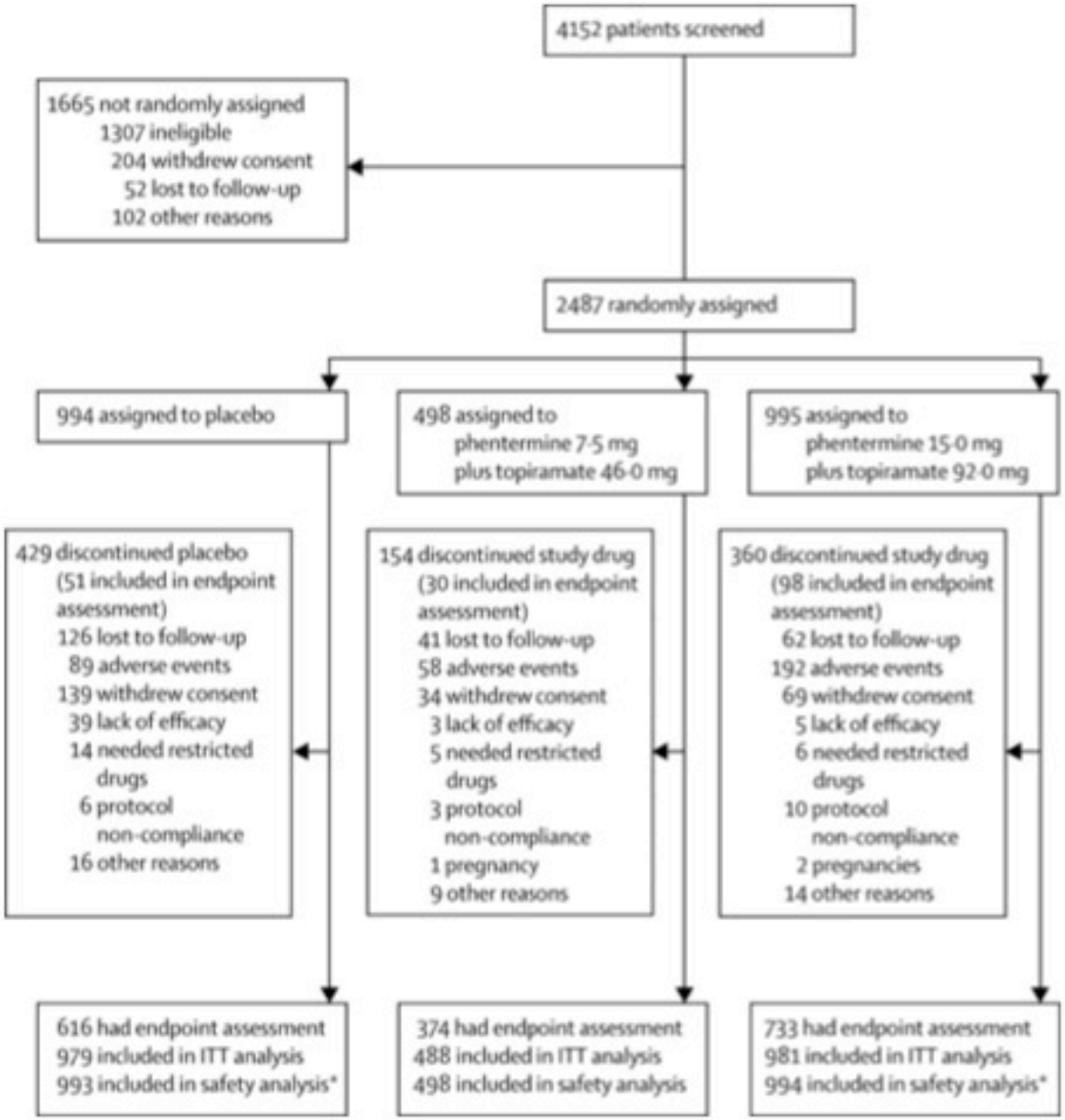
Kishore M Gadde, MD, David B Allison, PhD, Donna H Ryan, MD, Craig A Peterson, MS, Barbara Troupin, MD, Michael L Schwiers, MS and Wesley W Day, PhD

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

STUDIO
CONQUER
OB 303



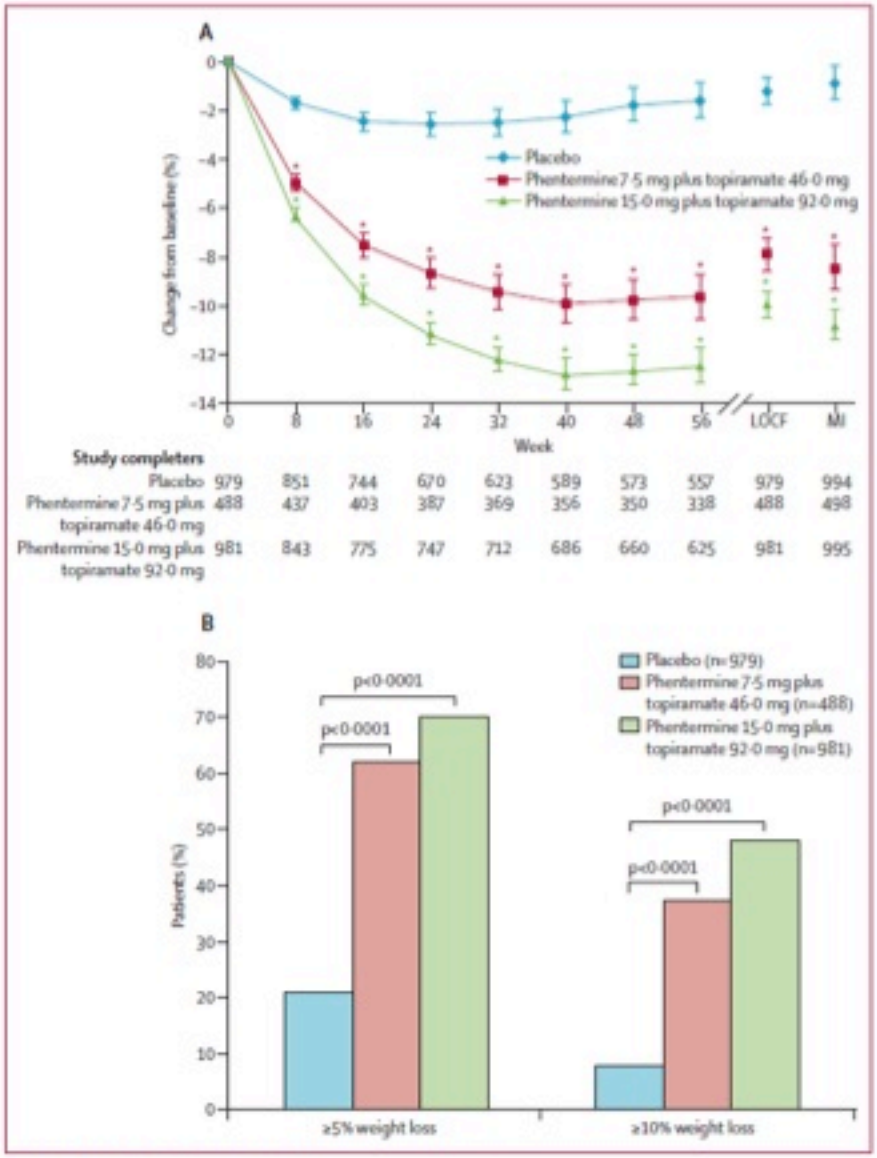


Figure 2: **Effects of phentermine plus topiramate on bodyweight**
(A) Least-squares mean change (95% CI) derived from three different statistical analyses. Weight change curves are plotted for completers by visit; shown to the right of the graph are data derived from the analyses of the intention-to-treat LOCF and MI. (B) Patients with at least 5% and at least 10% weight loss. LOCF=last observation carried forward. MI=multiple imputation.

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

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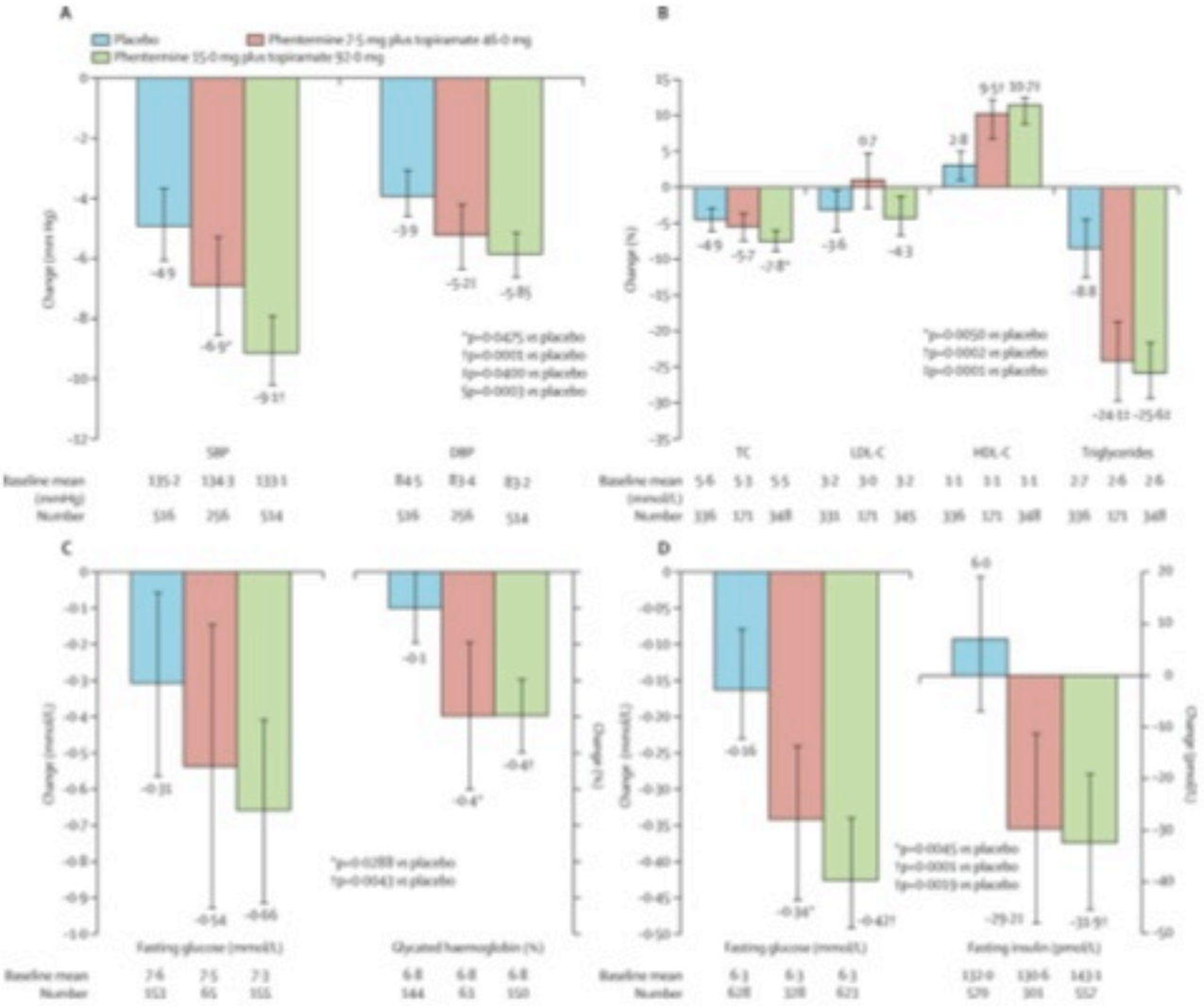


STUDIO CONQUER OB 303

Kishore M Gadde and coll

Table S3: Progression to type 2 diabetes* among patients without type 2 diabetes at baseline

	Placebo (n=834)	PHEN/TPM-CR 7·5/46 (n=430)	PHEN/TPM-CR 15/92 (n=828)
Development of diabetes, no. (%)	30 (3·6)	12 (2·8)	14 (1·7)
Subject years of treatment follow-up	667	388	747
Annualized incidence rate	4·5	3·1	1·9
Relative risk *vs* placebo (95% CI)		0·78 (0·40, 1·50)	0·47 (0·25, 0·88)

Table S4: Changes from baseline in concomitant antidiabetic medications

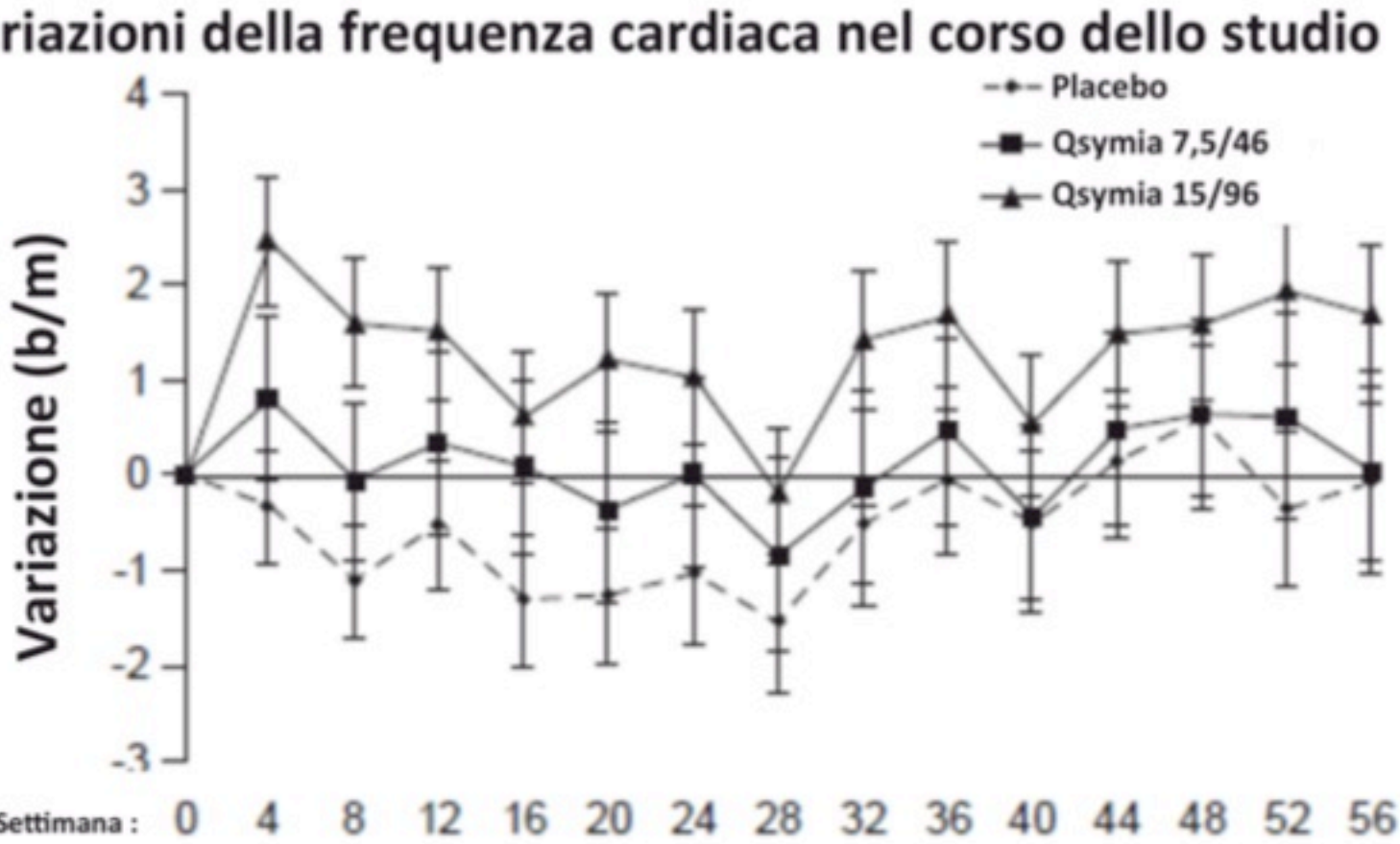
Number (%) with	Placebo (n=157)	PHEN/TPM-CR 7·5/46 (n=67)	PHEN/TPM-CR 15/92 (n=164)
Decrease	4 (2·5%)	2 (3·0%)	6 (3·7%)
No change	130 (82·8%)	62 (92·5%)	151 (92·1%)
Increase	23 (14·6%)	3 (4·5%)	7 (4·3%)

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

ELSEVIER

Kishore M Gadde and coll



Varazioni 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

	Placebo (n=993)	Phentermine 7·5 mg plus topiramate 46·0 mg (n=498)	p value	Phentermine 15·0 mg plus topiramate 92·0 mg (n=994)	p value
Dry mouth	24 (2%)	67 (13%)	<0·0001	207 (21%)	<0·0001
Paraesthesia	20 (2%)	68 (14%)	<0·0001	204 (21%)	<0·0001
Constipation	59 (6%)	75 (15%)	<0·0001	173 (17%)	<0·0001
Upper respiratory tract infection	128 (13%)	61 (12%)	0·7422	133 (13%)	0·7906
Nasopharyngitis	86 (9%)	53 (11%)	0·2204	98 (10%)	0·3947
Dysgeusia	11 (1%)	37 (7%)	<0·0001	103 (10%)	<0·0001
Insomnia	47 (5%)	29 (6%)	0·3832	102 (10%)	<0·0001
Headache	90 (9%)	35 (7%)	0·1983	101 (10%)	0·4467
Dizziness	31 (3%)	36 (7%)	0·0005	99 (10%)	<0·0001
Sinusitis	67 (7%)	34 (7%)	1·0000	85 (9%)	0·1511
Back pain	49 (5%)	28 (6%)	0·6199	72 (7%)	0·0386
Nausea	42 (4%)	18 (4%)	0·6754	68 (7%)	0·0139
Fatigue	50 (5%)	22 (4%)	0·7010	67 (7%)	0·1270
Diarrhoea	48 (5%)	32 (6%)	0·2229	58 (6%)	0·3690
Blurred vision	36 (4%)	20 (4%)	0·7729	60 (6%)	0·0157
Urinary tract infection	37 (4%)	26 (5%)	0·1753	54 (5%)	0·0855
Arthralgia	54 (5%)	23 (5%)	0·5373	44 (4%)	0·3025
Bronchitis	43 (4%)	22 (4%)	1·0000	52 (5%)	0·4004
Psychiatric adverse events†					
Depression	29 (3%)	14 (3%)	0·9054	39 (4%)	0·2188
Anxiety	21 (2%)	9 (2%)	0·6899	41 (4%)	0·0100
Irritability‡	8 (<1%)	13 (3%)	0·0053	34 (3%)	<0·0001
Time to onset (days; median, IQR)	92 (26–164)	36 (8–138)	0·0988	29 (17–118)	0·0049
Duration (days; median, IQR)	44 (17–121)	35 (11–81)	0·2989	29 (12–63)	0·0252
Resolution among patients discontinuing drug	4/5 (80%)	10/10 (100%)	0·3333	33/37 (89%)	0·4876
Cognitive adverse events§					
Disturbance in attention	7 (<1%)	10 (2%)	0·0362	35 (4%)	<0·0001
Time to onset (days; median, IQR)	22 (8–119)	23 (10–100)	0·8958	25 (11–51)	0·8223
Duration (days; median, IQR)	39 (13–76)	51 (8–149)	0·4452	36 (18–81)	0·7353
Resolution among subjects discontinuing drug	3/3 (100%)	2/2 (100%)	NA	21/21 (100%)	NA

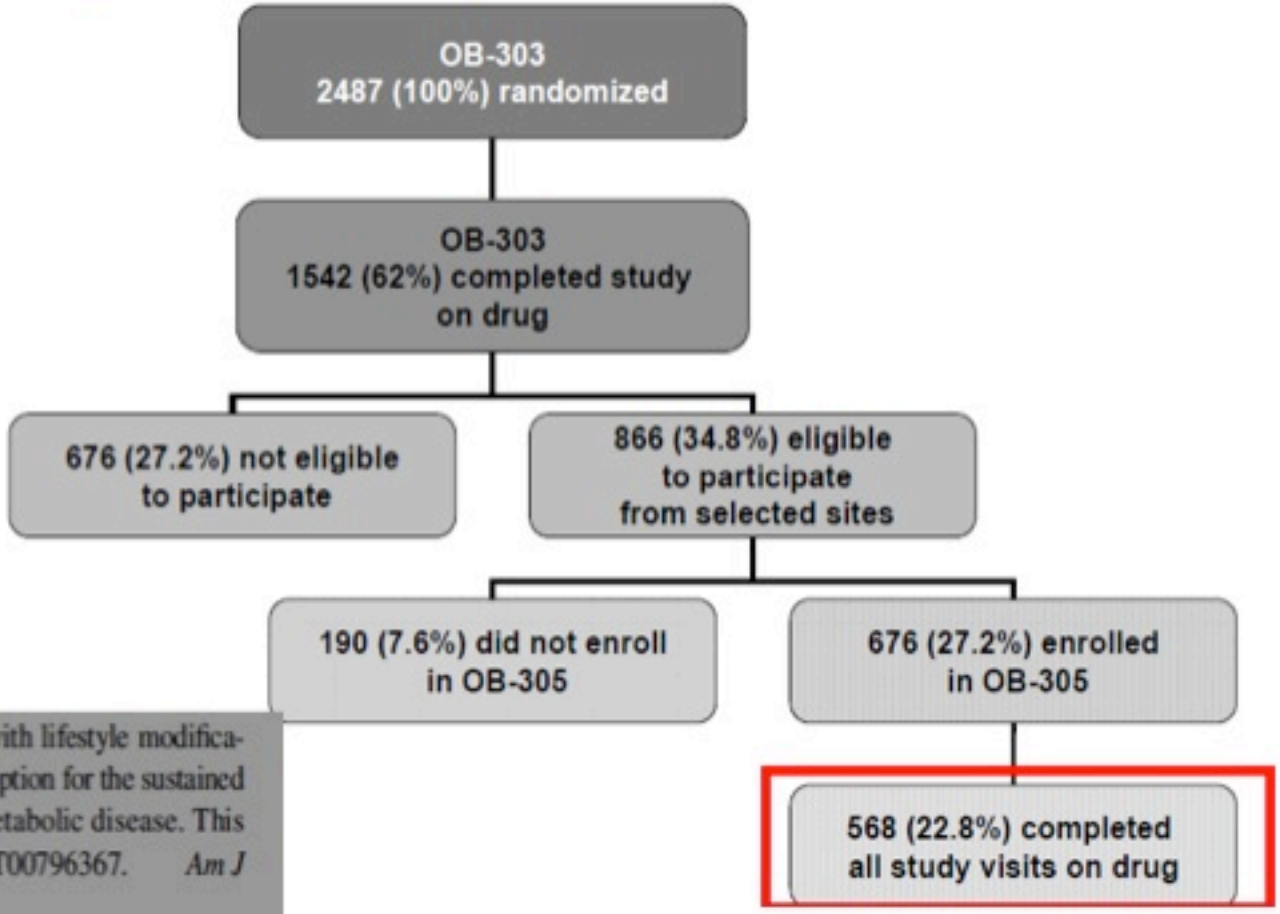
Data are number (%) or n/N (%), unless otherwise indicated. p values are for comparisons of phentermine plus topiramate with placebo. NA=not applicable. *Psychiatric and cognitive adverse events arising at a frequency of 2% or more, and other adverse events arising at a frequency of 5% or more with any 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 event category although it is classified as a general disorder in MedDRA. §Including the preferred terms from MedDRA: disturbance in attention, memory impairment, amnesia, confusional state, cognitive disorder, bradyphrenia, 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[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



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

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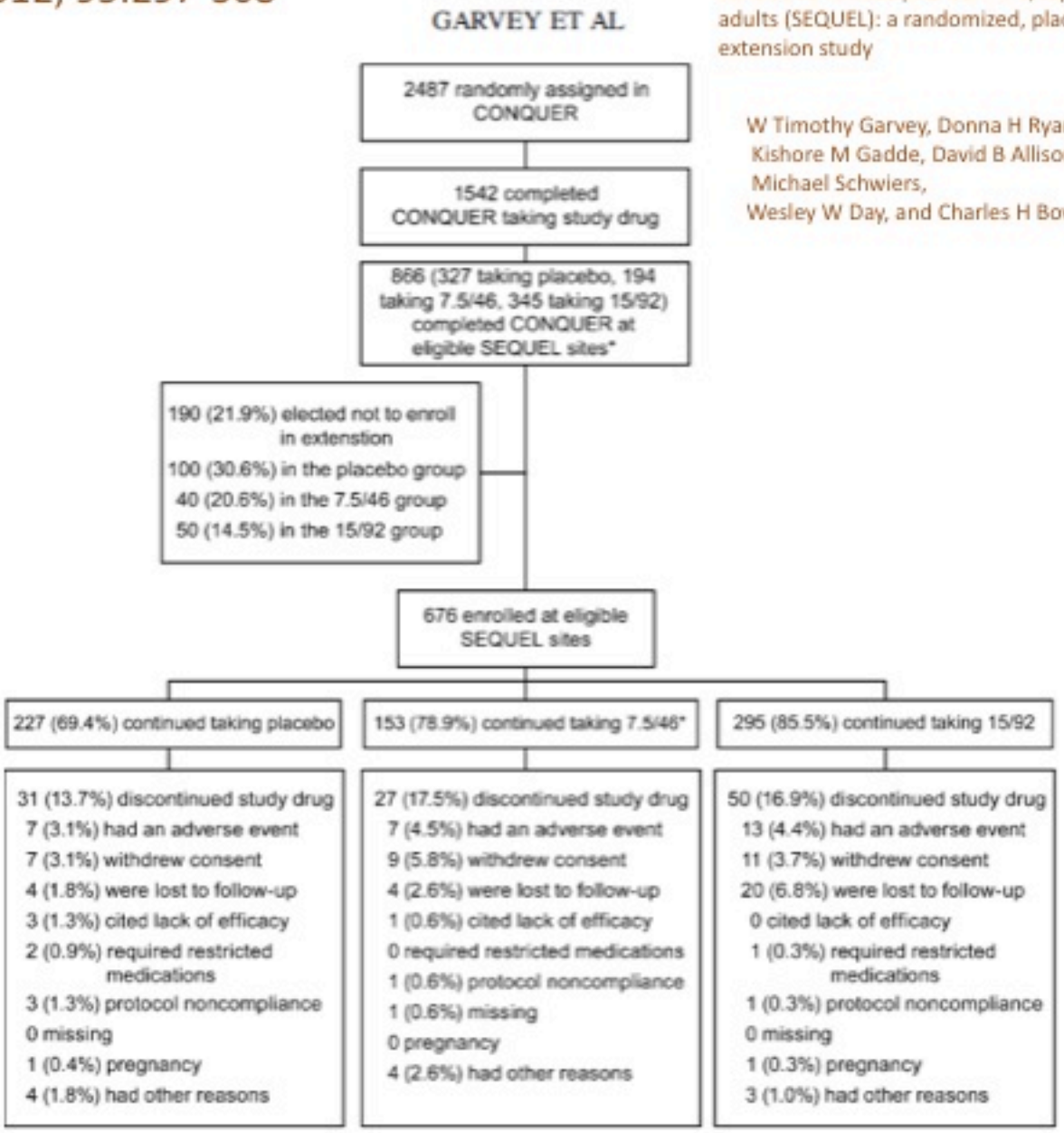
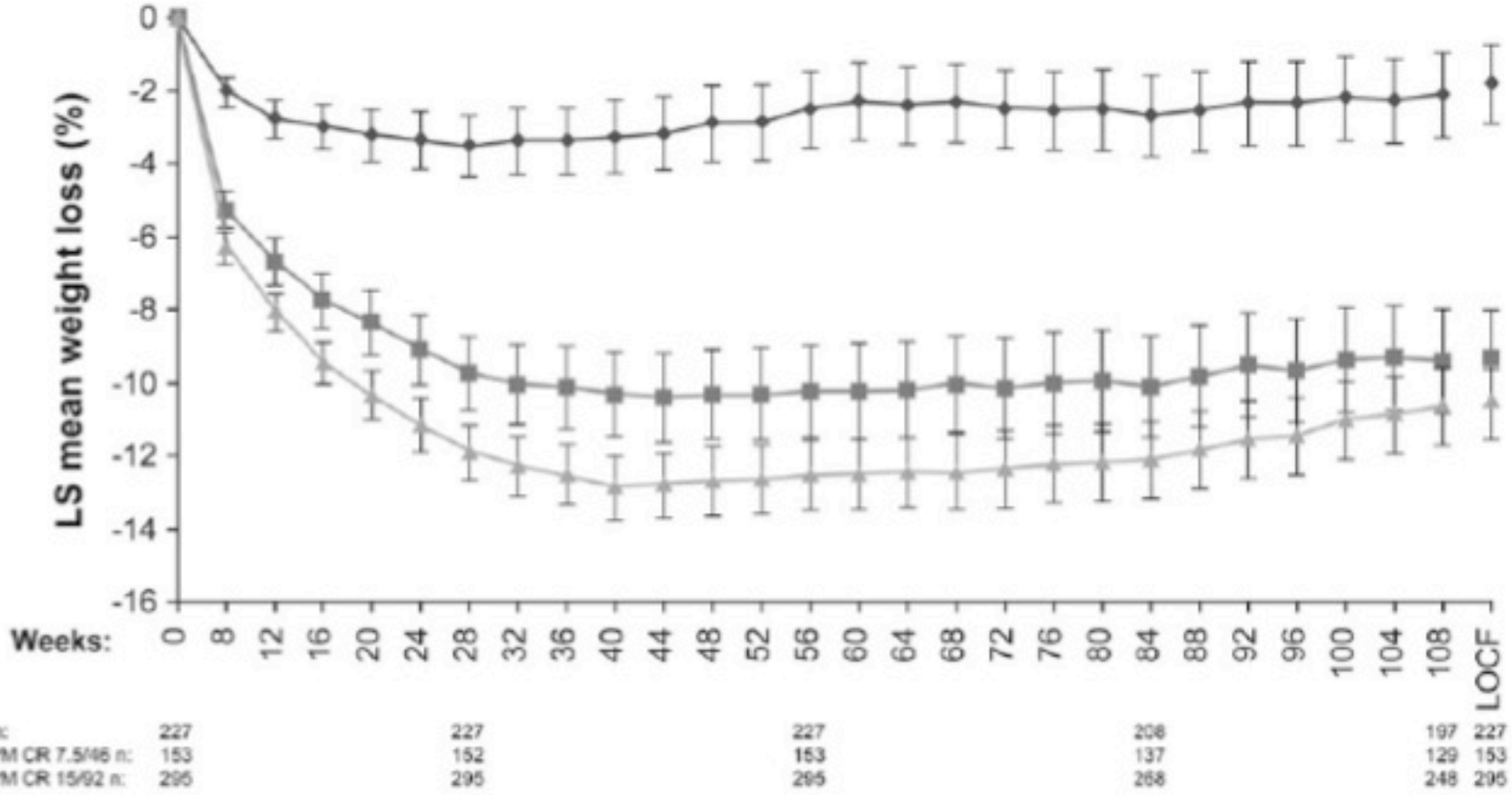


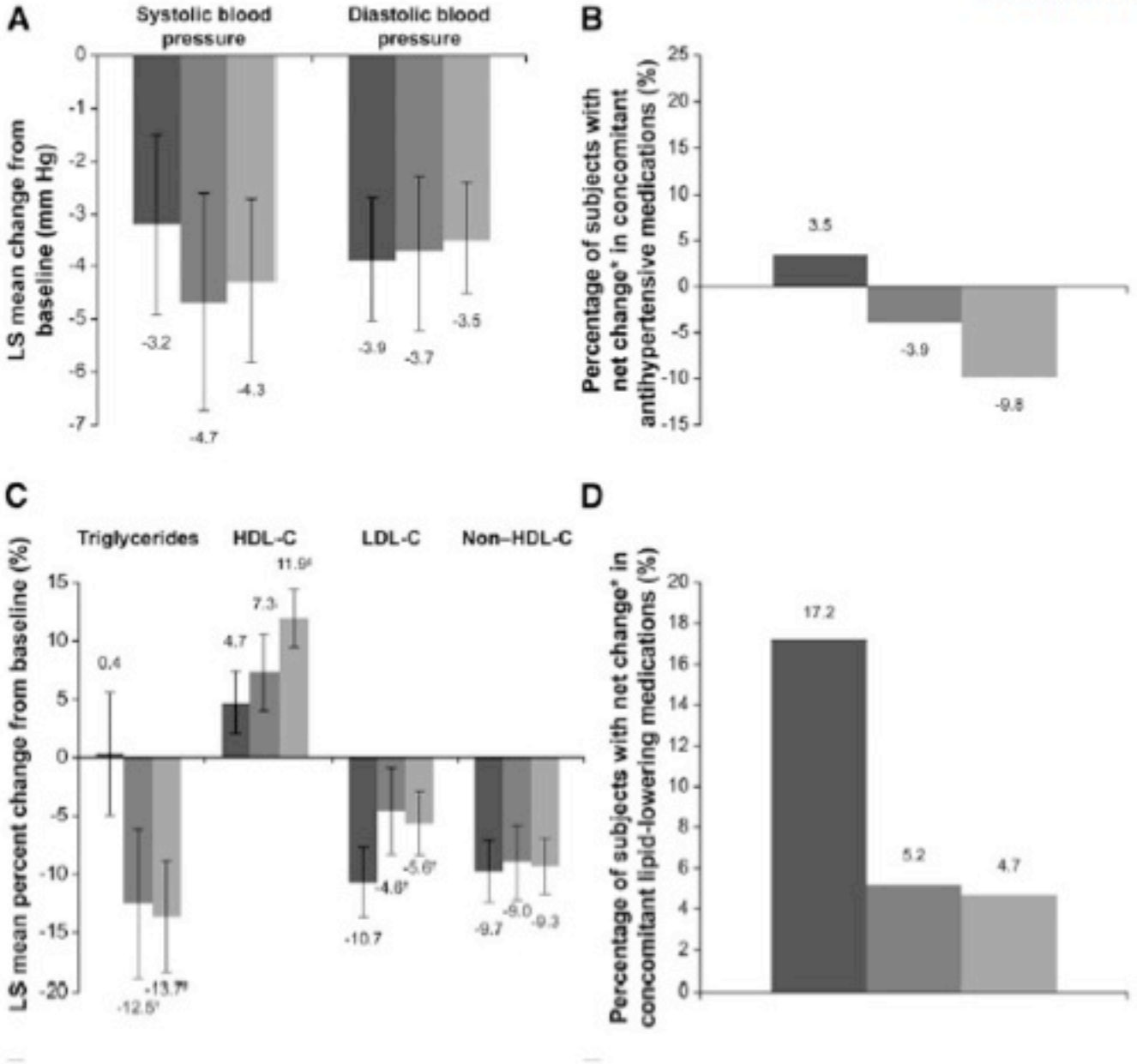
GARVEY ET AL


LS mean weight loss (%)
0
-2
-4
-6
-8
-10
-12
-14
-16
Weeks:
0 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 LOCF
Placebo n: 227 227 227 208 197 227
PHEN/TPM CR 7.5/46 n: 153 152 153 137 129 153
PHEN/TPM CR 15/92 n: 295 295 295 268 248 295
Placebo
PHEN/TPM CR 7.5/46
PHEN/TPM CR 15/92

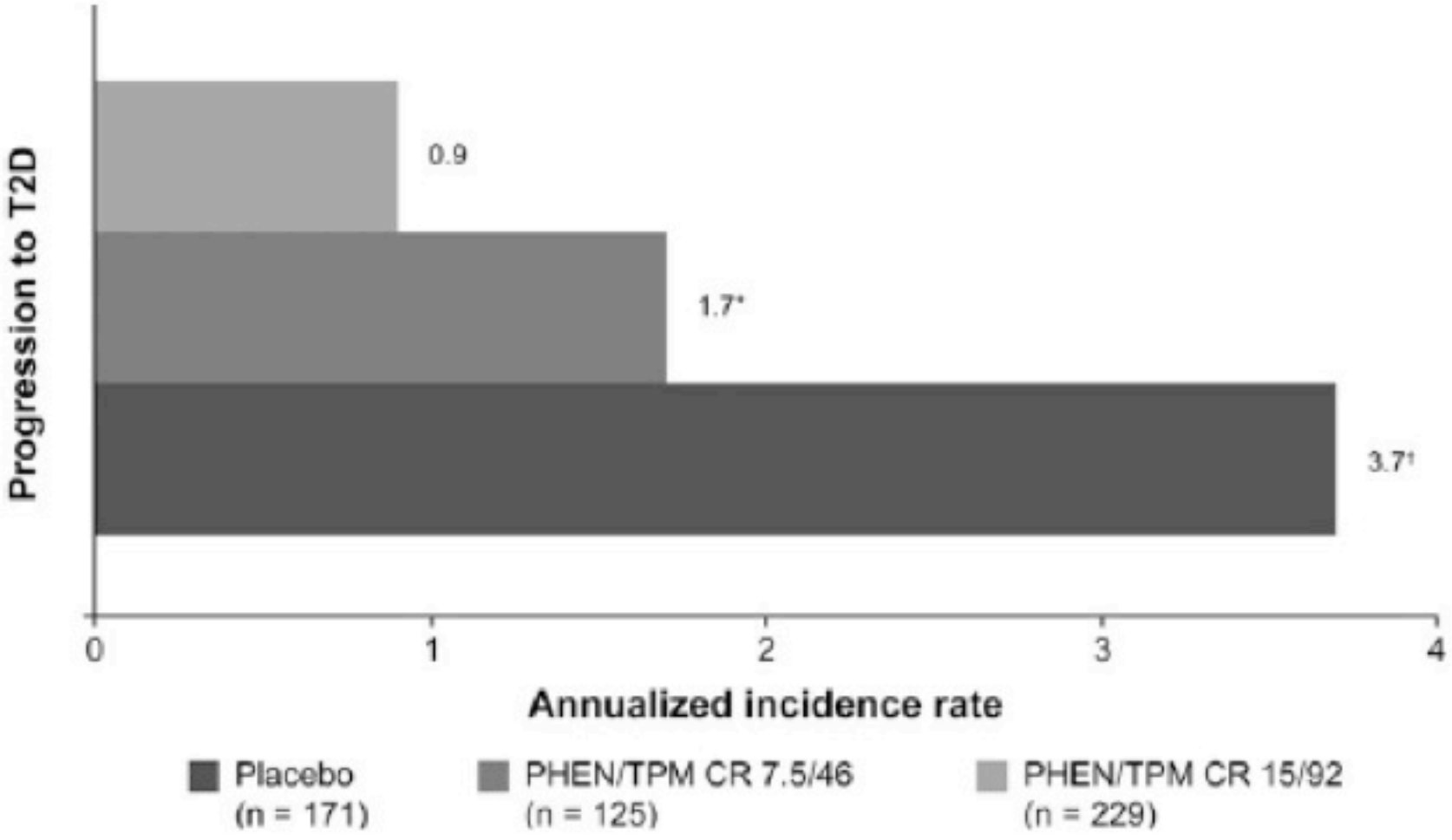
2-y WEIGHT LOSS WITH PHENTERMINE/TOPIRAMATE CR

SEQUEL STUDY

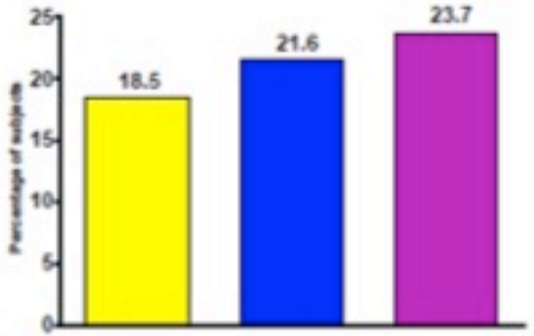
Am J Clin Nutr 2012; 95:297-308



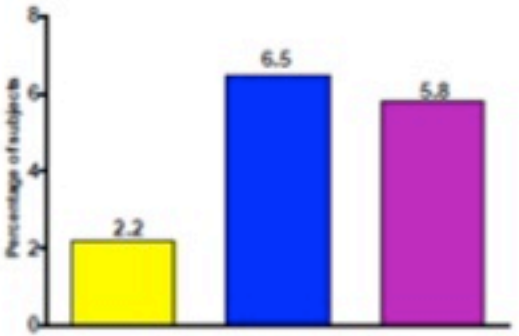
SEQUEL STUDY
Am J Clin Nutr 2012; 95:297-308



Safety Events of Interest: Two-year Cohort



Psychiatric disorders

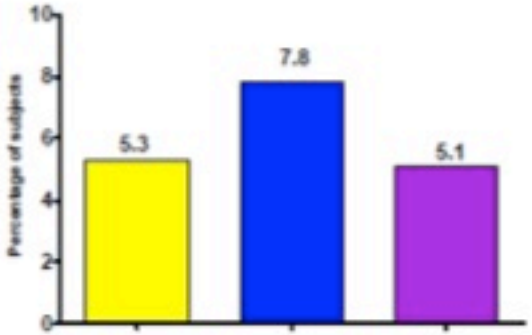


Cognitive disorders

Placebo

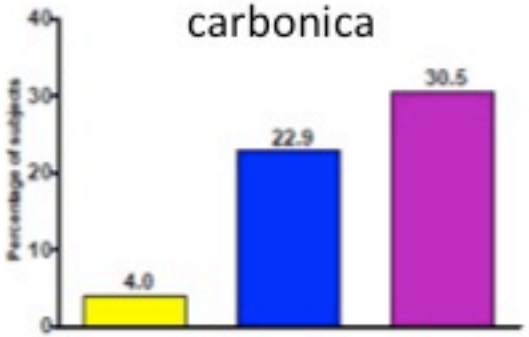
Mid-dose PHEN/TPM

High-dose PHEN/TPM



Cardiovascular disorders

Topiramato inibisce anidrasi carbonica



Bicarb <21 mEq/L

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

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

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)

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

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

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

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 (Qysmia)

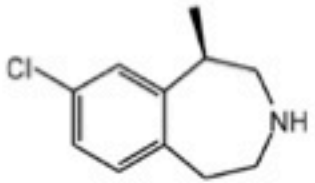
VIVUS Receives Decision Regarding Qsiva Appeal

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.

Lorcaserina

La molecola



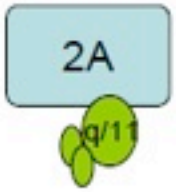
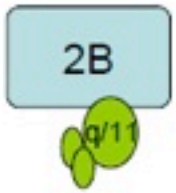
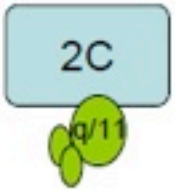
In data 27 giugno 2012 la FDA ha autorizzato l'immissione in commercio di lorcaserina per il trattamento di soggetti obesi o con BMI ≥ di 27 in presenza di comorbilità

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 cerebrali 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

5HT2 subtype	Distribution/Function	
	CNS	**Periphery**
	**Drug-induced hallucinogenic responses** Anxiety, behavior, locomotion	Liver, renal mesangium mitogenesis Vasoactive (pulmonary/coronary vessels) Adipocyte differentiation, Platelet aggregation, enteric neurotransmitter
	Motor behavior, Anxiety, cerebrovascular tone	**Drug-induced valvulopathy** Pulmonary vascular remodeling/hypertension Hepatocellular mitogen
	**Appetite suppression** Locomotion, Anxiety DA output, stress response	Limited expression

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.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

Steven R. Smith, M.D., Neil J. Weissman, M.D., Christen M. Anderson, M.D., Ph.D., Matilde Sanchez, Ph.D., Emil Chuang, M.D., Scott Stubbe, M.B.A., Harold Bays, M.D., William R. Shanahan, M.D., and the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group

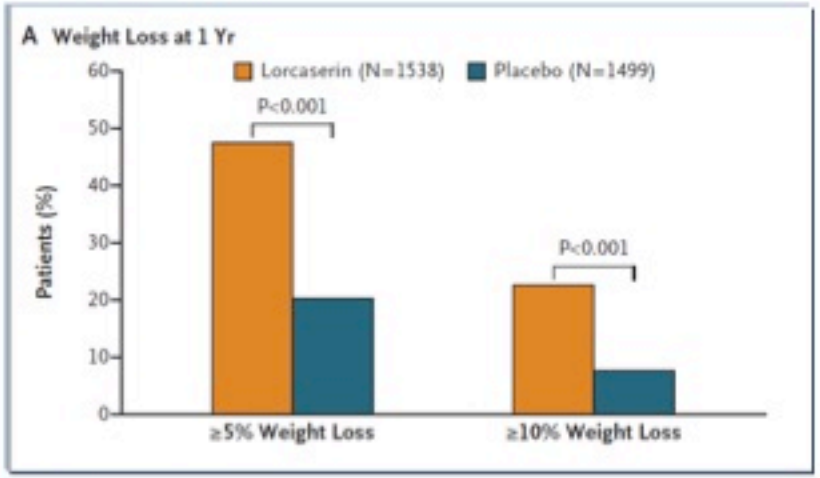
3182 pz obesi (BMI 30 – 45)
o sovrappeso/obesi (BMI 27–45) con almeno una comorbilità (ipertensione, dislipidemia, malattia CV, IGT, OSAS

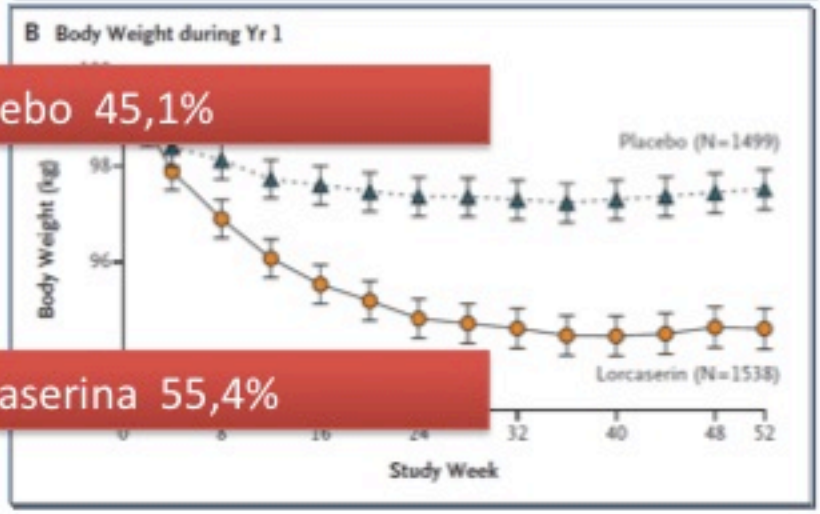
Criteri di esclusione
- insufficienza mitralica moderata, insufficienza aortica lieve
- diabete mellito, PAS > 140 PAD > 90
- Depressione fino a 2 anni prima con necessità di terapia farmac.
- Gravidanza e lattazione

ORIGINAL ARTICLE

Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

Perdita di peso dopo 1 anno





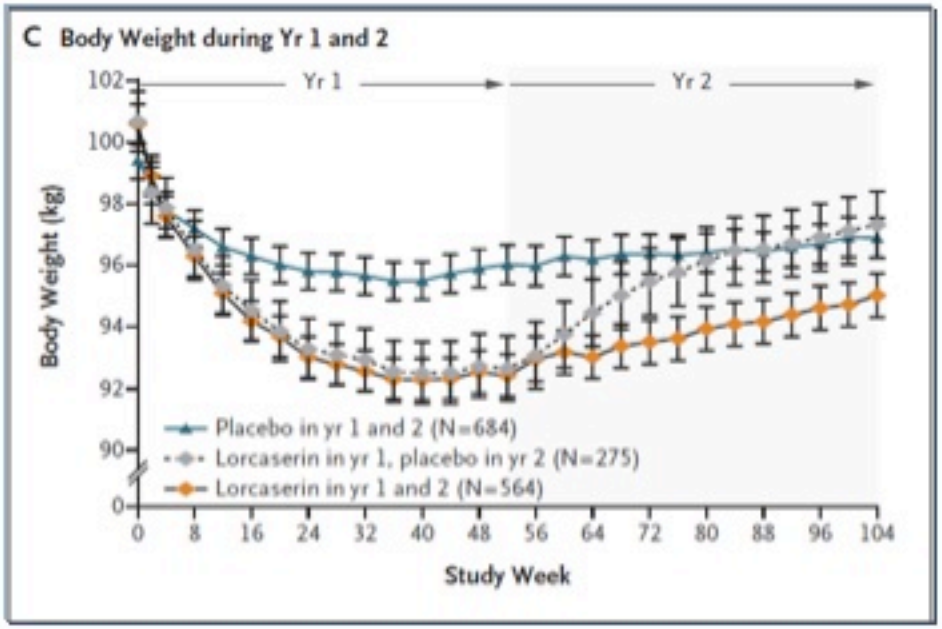
Completers placebo 45,1%

Completers lorcaserina 55,4%

ORIGINAL ARTICLE

Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

Perdita di peso dopo2 anni



ORIGINAL ARTICLE

Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

End Point	Intention-to-Treat Analysis with LOCF Imputation		
	Lorcaserin (N=1538)	Placebo (N=1499)	P Value
Coprimary end points			
Loss of ≥5% of body weight			
Patients (%)	47.5	20.3	<0.001
Weight change (kg)	−5.8±0.2	−2.2±0.1	<0.001
Loss of ≥10% of body weight (%)	22.6	7.7	<0.001
Key secondary end points			
Waist circumference (cm)	−6.8±0.2	−3.9±0.2	<0.001
Body-mass index†	−2.09±0.06	−0.78±0.05	<0.001
Blood pressure (mm Hg)			
Systolic	−1.4±0.3	−0.8±0.3	0.04
Diastolic	−1.1±0.2	−0.6±0.2	0.01
Cholesterol (%)			
Total	−0.90±0.33	0.57±0.34	0.001
LDL	2.87±0.56	4.03±0.58	0.049
HDL	0.05±0.33	−0.21±0.34	0.72
Triglycerides (%)	−6.15±1.03	−0.14±0.99	<0.001
Fasting glucose (mg/dl)	−0.8±0.3	1.1±0.3	<0.001
Fasting insulin (μU/ml)	−3.33±0.38	−1.28±0.45	0.001
HOMA-IR	−0.41±0.03	−0.17±0.03	<0.001
Glycated hemoglobin (%)	−0.04±0.01	0.03±0.01	<0.001
High-sensitivity CRP (mg/liter)	−1.19±0.18	−0.17±0.19	<0.001
Fibrinogen (mg/dl)	−21.5±2.2	−10.6±2.1	0.001
IWQOL-Lite score	12.4±0.4	10.7±0.4	<0.001

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) CIV

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) or
- 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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2013
EMA/309180/2013
EMEA/H/C/002597

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.

Withdrawal of the marketing authorisation application for Belviq (lorcaserin)

Bupropione - Naltrexone

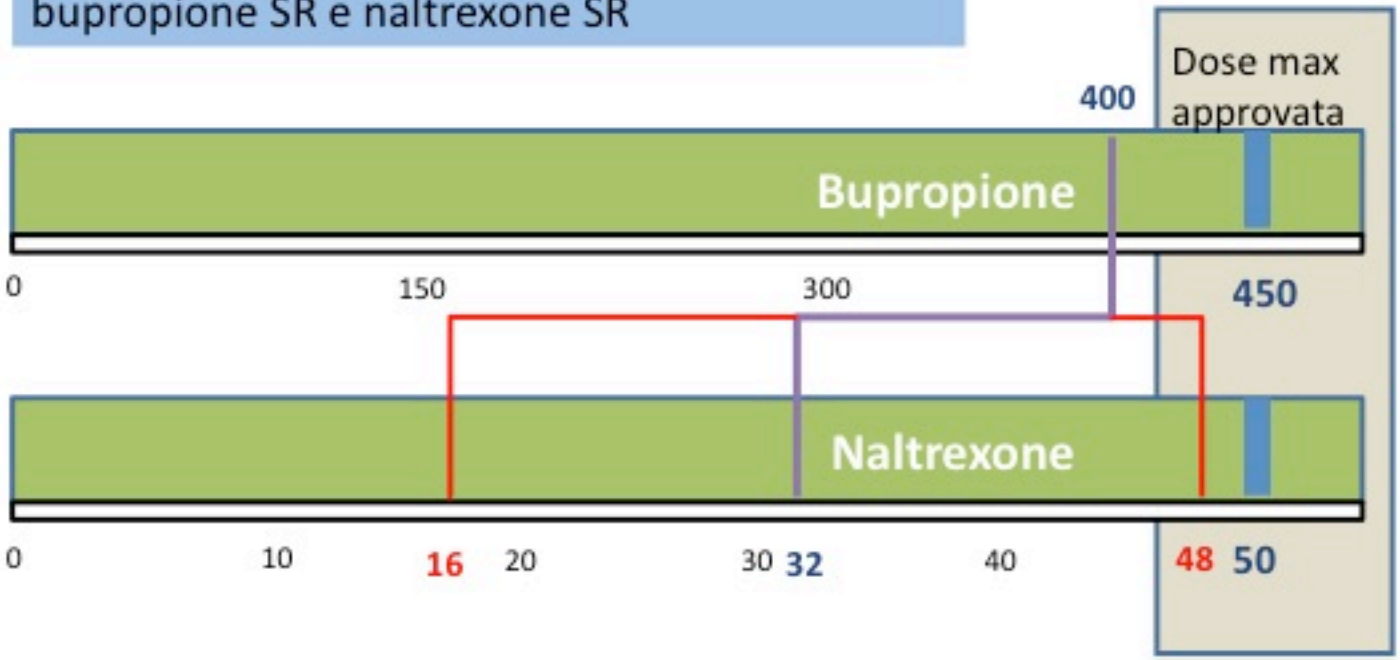
Bupropione

- 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

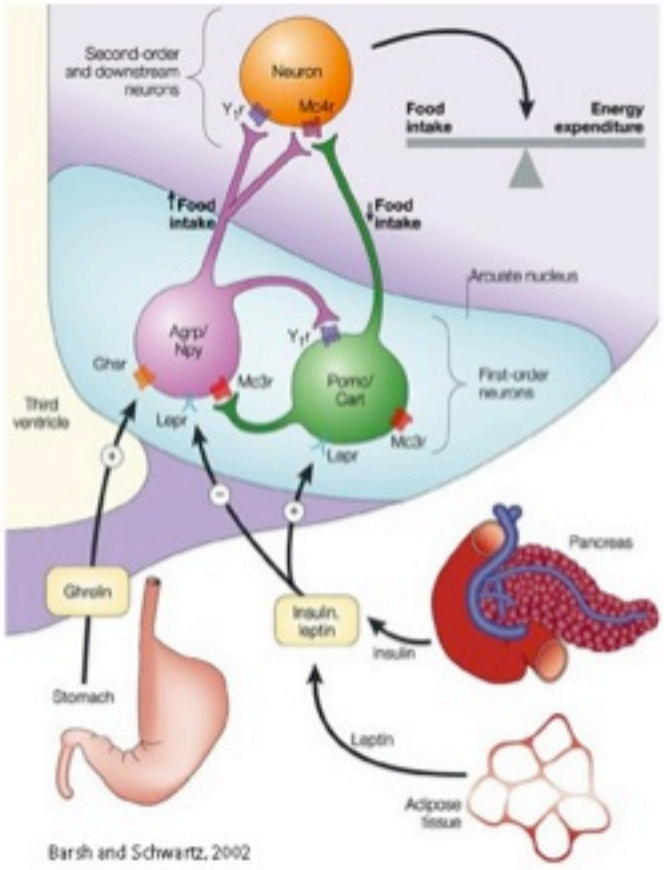
- Farmaco antagonista oppiacei
- In commercio dal 1984
- AIC: disintossicazione da dipendenze (alcool, oppiacei)
- Dose massima giornaliera 50 mg

Somministrazione due volte al giorno di bupropione SR e naltrexone SR



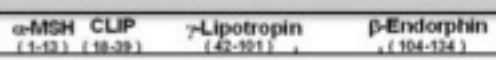
Bupropione - Naltrexone

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



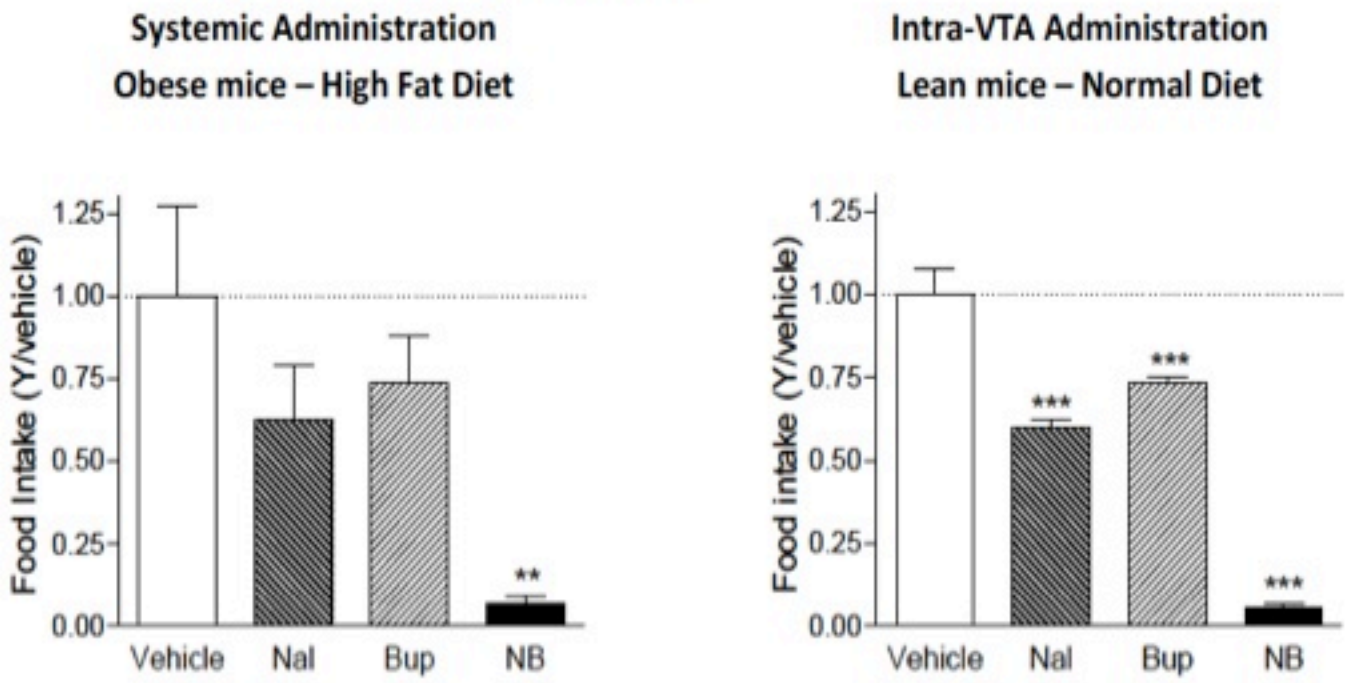
I neuroni POMC rilasciano simultaneamente beta-endorfina che svolge un feed-back negativo sui neuroni POMC stessi

α-Endorphin

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**



** 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.

ORIGINAL ARTICLE

Endocrine Care

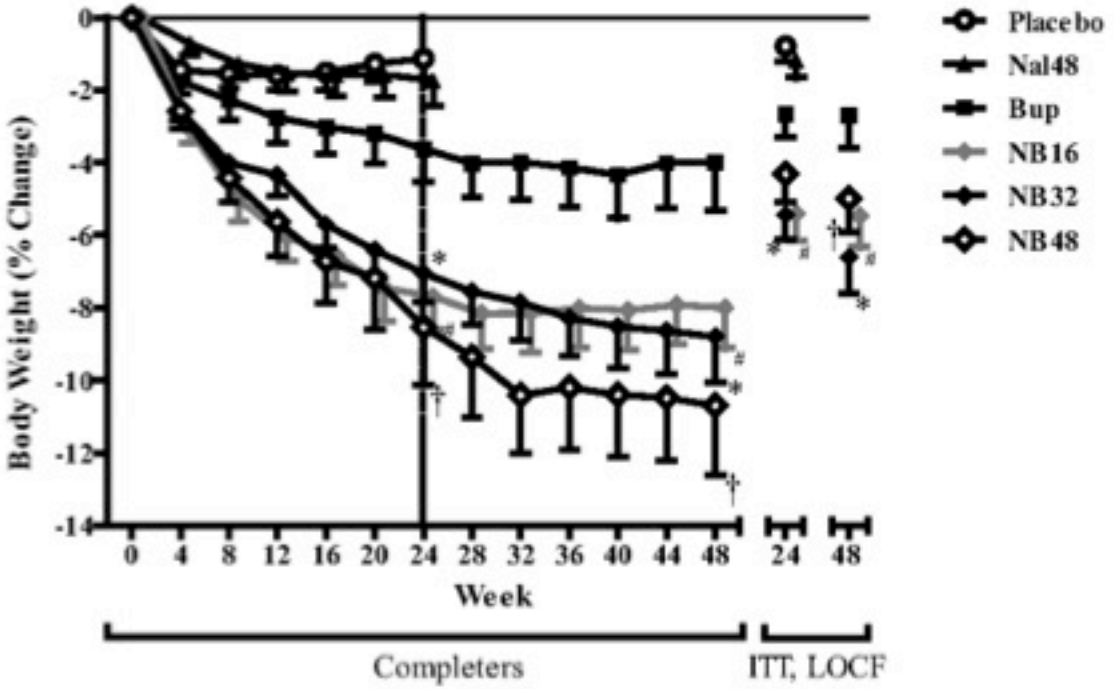
Comparison of Combined Bupropion and Naltrexone Therapy for Obesity with Monotherapy and Placebo

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

jcem.endojournals.org J Clin Endocrinol Metab. December 2009, 94(12):4898–4906

Studio richiesto da FDA per le associazioni di più farmaci che serve a dimostrare che l'associazione è più potente dei singoli principi attivi

Percent change in body weight.



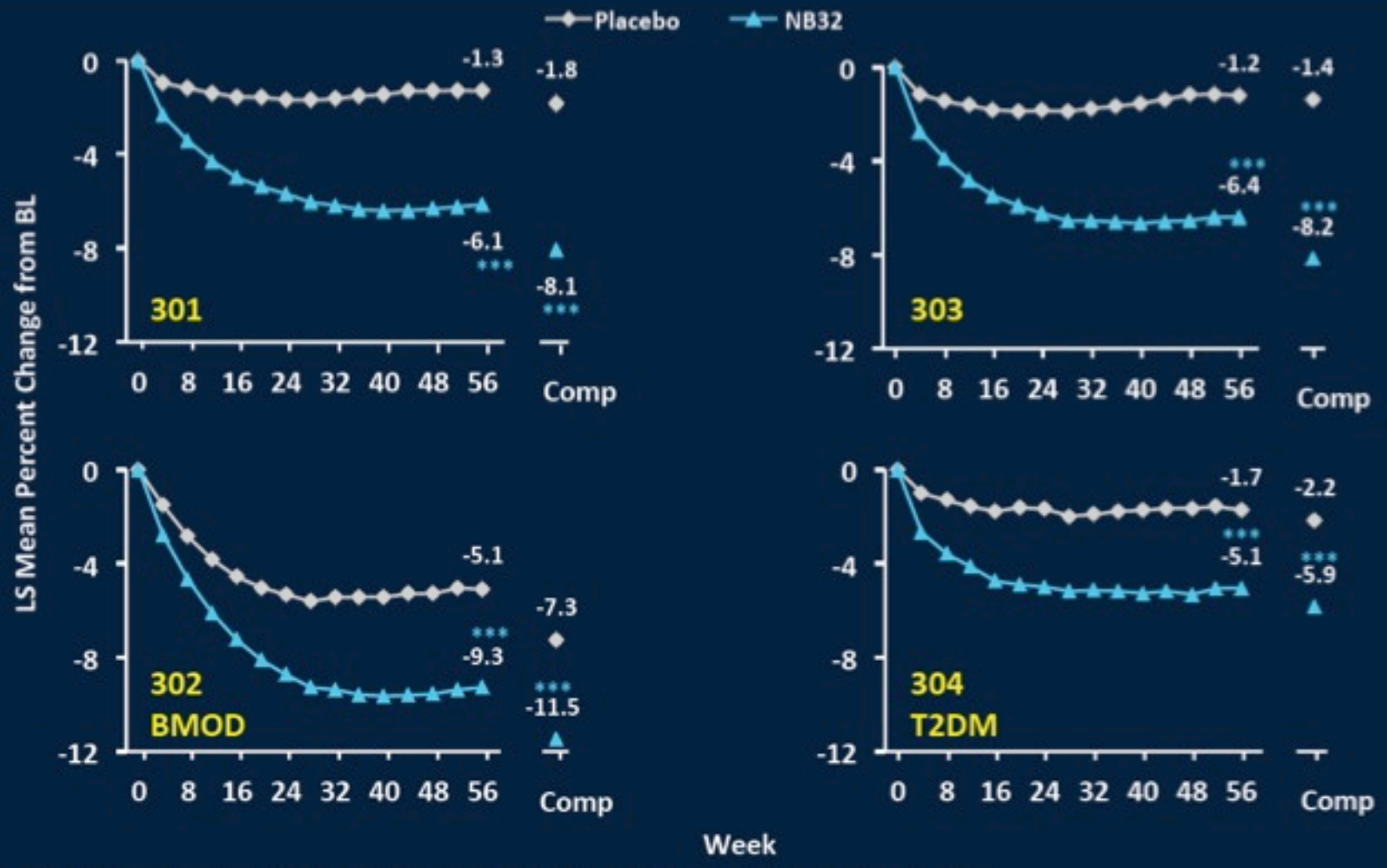
# P < 0.05 for NB16 vs. placebo, Nal 48 and Bup
* P < 0.05 for NB32 vs. placebo, Nal 48 and Bup
† P < 0.05 for NB48 vs. placebo, Nal 48 and Bup
Statistical significance indicated for Week 24 and Week 48 only . Dashed line indicates primary endpoint (Week 24).

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

The Journal of Clinical Endocrinology & Metabolism

Contrave® Produced Rapid and Sustained Weight Loss Up to 56 Weeks



***p<0.001 vs placebo; 303 based on weighted ANCOVA; completers at endpoint

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

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.

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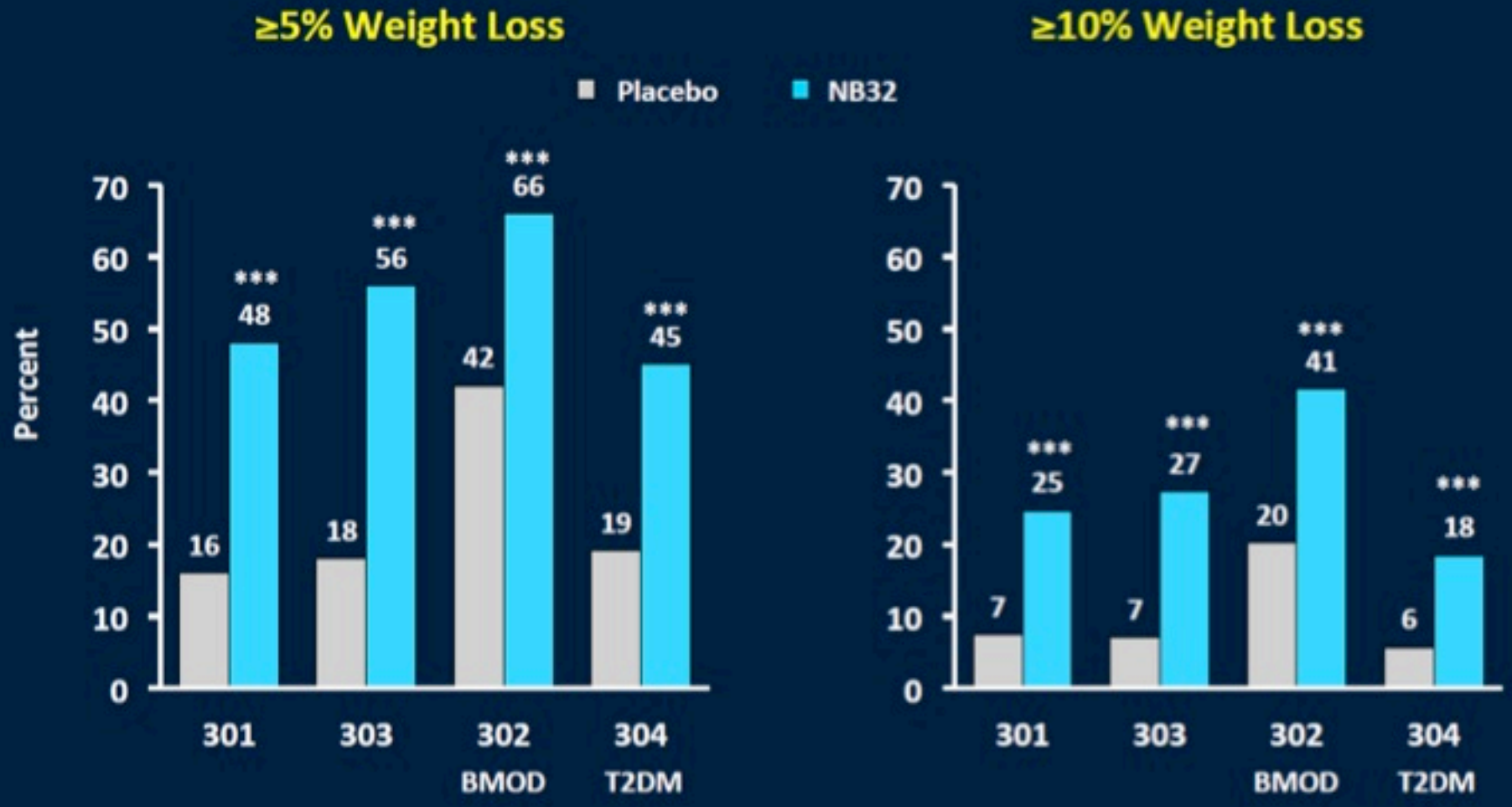
Significantly More Subjects Achieved Meaningful Weight Loss with Contrave®



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
  - Constipation
  - Headache
  - Vomiting
  - Dizziness
  - Insomnia
  - Dry mouth
  - 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

Bupropione - Naltrexone

ARTICLES
INTERVENTION AND PREVENTION

nature publishing group

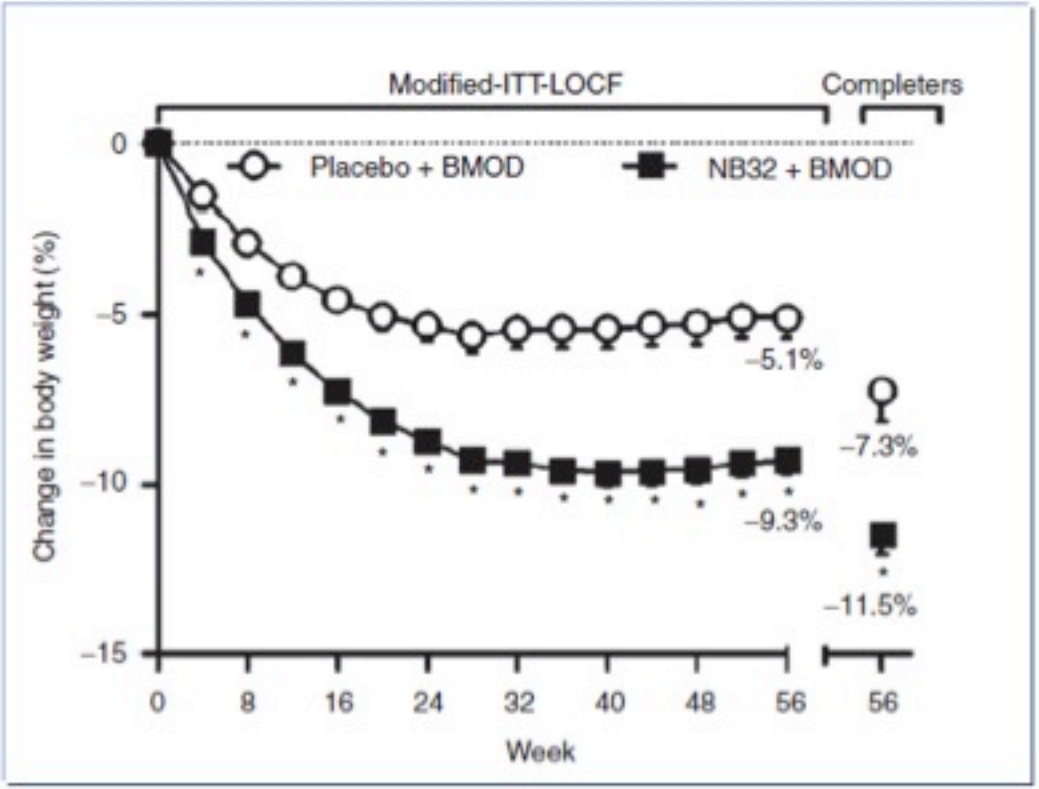
Weight Loss With Naltrexone SR/Bupropion SR Combination Therapy as an Adjunct to Behavior Modification: The COR-BMOD Trial

Thomas A. Wadden[1], John P. Foreyt[2], Gary D. Foster[3], James O. Hill[4], Samuel Klein[5], Patrick M. O'Neil[6], Michael G. Perri[7], F. Xavier Pi-Sunyer[8], Cheryl L. Rock[9], Janelle S. Erickson[10], Holly N. Maier[11], Dennis D. Kim[11] and Eduardo Dunayevich[11]

Received 24 December 2009; accepted 24 May 2010; published online 17 June 2010. doi:10.1038/oby.2010.147

Table 1 Baseline characteristics of study participants

Variable	Placebo + BMOD *N* = 202	NB32 + BMOD *N* = 591
Gender (% female)	91.6	89.3
Age (years)	45.6 ± 11.4	45.9 ± 10.4
BMI (kg/m^2)	37.0 ± 4.2	36.3 ± 4.2
Weight (kg)	101.9 ± 15.0	100.2 ± 15.4



LIGHTSTUDY

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)

LIGHTSTUDY

PRNewswire

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

Aprile 2013

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

Maggio 2013

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.

Figure A
Qsymia (3.75 mg/23 mg)
Cap and body are purple with white printing

Figure B
Qsymia (7.5 mg/46 mg)
Cap is purple with white printing and the body is yellow with black printing

Figure C
Qsymia (11.25 mg/69 mg)
Cap and body are yellow with black printing

Figure D
Qsymia (15 mg/92 mg)
Cap is yellow with black printing and the body is white with black printing

Review

Bari,
7-10 novembre 2013

Weight Beneficial Treatments for Type 2 Diabetes

L. F. Meneghini, D. Orozco-Beltran, K. Khunti, S. Caputo, T. Damçi, A. Liebl, and S. A. Ross

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

	Expected reduction in HbA1c with monotherapy (%)	Expected weight Δ over 6 months (kg)	Impact on PPG	Impact on FPG
α-Glucosidase inhibitors (acarbose)	0.5–0.8	Weight neutral	++	–
Amylin analogs	0.5–1.0	Weight neutral or loss 0 to −1.5 kg	++ to +++	+
Basal insulin				
Detemir	1.5–3.5	Weight neutral or gain 0 to +1.5 kg	+	++ to +++
Glargine	1.5–3.5	Weight gain up to +4 kg	+	++ to +++
GLP-1 analogs	0.5–1.0	Weight loss −1.0 to −3.0 kg	++ to +++	+ to ++
DPP-4 inhibitors	0.5–0.8	Weight neutral	++	+
Metformin	1.0–2.0	Weight neutral or loss 0 to −1.5 kg	+	++
SU	1.0–2.0	Weight gain +1 to +5 kg	++	++
TZD	0.5–1.4	Weight gain: +3 kg	+	++

LIRAGLUTIDE

Bari,
7-10 novembre 2013

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail

Text Size

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
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

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).

Condition	Intervention	Phase
Metabolism and Nutrition Disorder Obesity	Drug: liraglutide Drug: placebo	Phase 3

Benefits of Liraglutide Treatment in Overweight and Obese Older Individuals With Prediabetes

Sun H. Kim, MD[1]
Fahim Abbasi, MD[1]
Cindy Lamendola, MSN[1]
Alice Liu, MD[1]
Danit Ariel, MD[1]
Patricia Schaaf, MS, RD[1]
Kaylene Grove, BS[1]
Vanessa Tomasso, BS[1]
Hector Ochoa, BS[1]
Yehenq V. Liu, BS, MPH[2,3]
Yii-Der Ida Chen, PhD[2,3]
Gerald Reaven, MD[1]

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

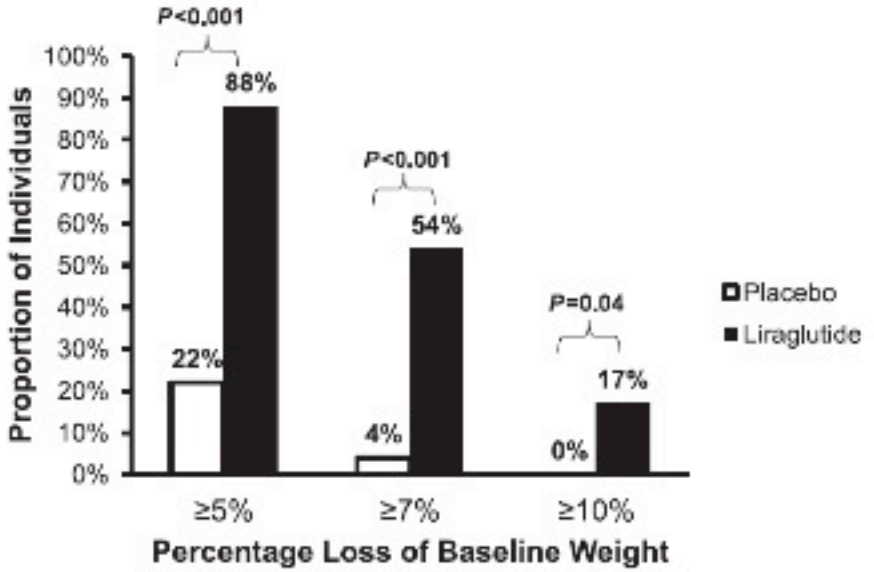


Figure 1—*Proportion of individuals who lost at least 5, 7, and 10% of baseline weight. Liraglutide treatment was associated with greater degree of weight loss compared with placebo.*

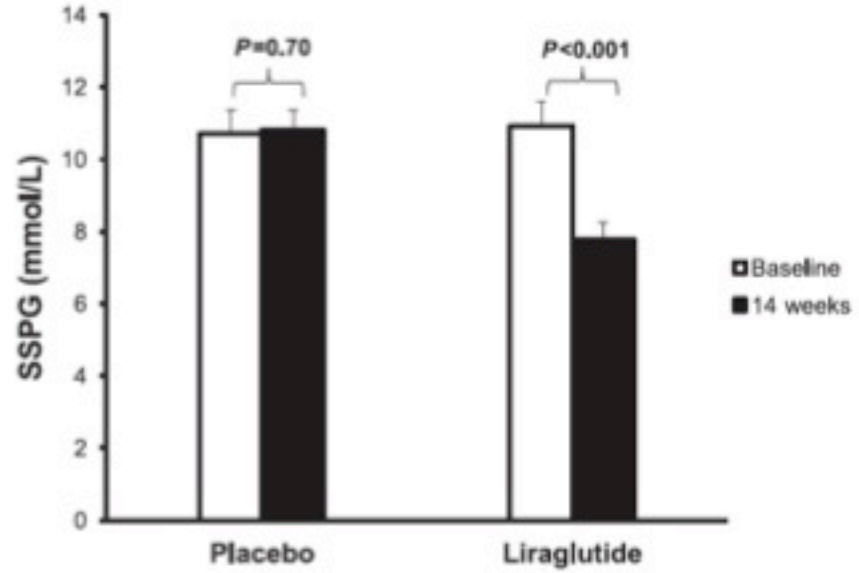


Figure 2—*Insulin resistance (SSPG) at baseline and after 14 weeks of liraglutide or placebo treatment. Insulin resistance significantly improved following liraglutide treatment but not placebo.*

Diabetes Care 36:3276–3282, 2013

Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials

Bari,
7-10 novembre 2013

Trial	No of patients: GLP-1R agonist group	No of patients: Control group	Mean change (standard deviation): GLP-1R agonist group	Mean change (standard deviation): Control group	Weight (%)	Weighted mean difference (95% CI)
Bergenstal 2010	160	166	-2.3 (3.0)	-0.8 (0.3)	4.98	-1.50 (-1.97 to -1.03)
Buse 2004	129	123	-1.6 (3.4)	0.6 (3.3)	4.74	-1.00 (-1.83 to -0.17)
Kendall 2005	241	247	-1.6 (3.1)	-0.9 (3.1)	4.93	-0.70 (-1.26 to -0.14)
Pratley 2010	221	219	-3.4 (3.0)	-1.0 (1.8)	4.98	-2.42 (-2.88 to -1.96)
Moretto 2008	78	78	-3.1 (2.7)	-1.4 (2.7)	4.74	-1.70 (-2.53 to -0.87)
Nauck 2009	242	122	-2.8 (0.2)	-1.5 (0.3)	5.09	-1.30 (-1.36 to -1.24)
Garber 2009	246	248	-2.5 (7.8)	1.0 (7.9)	4.21	-3.50 (-4.89 to -2.11)
Diamant 2010	233	223	-2.6 (3.1)	1.4 (3.0)	4.93	-4.00 (-4.55 to -3.45)
DeFronzo 2010	45	45	-2.8 (3.4)	1.5 (3.4)	4.21	-4.30 (-5.69 to -2.91)
Russell-Jones 2009	230	114	-1.8 (5.0)	-0.4 (4.1)	4.59	-1.38 (-2.38 to -0.38)
Heine 2005	282	267	-2.3 (3.9)	1.8 (4.0)	4.86	-4.10 (-4.76 to -3.44)
Astrup 2009	93	98	-7.2 (0.5)	-2.8 (0.5)	5.08	-4.40 (-4.54 to -4.26)
Elkin 2010	20	20	-3.2 (0.5)	-1.6 (0.9)	4.99	-1.60 (-2.04 to -1.16)
Davies 2009	118	117	-2.7 (3.4)	3.0 (3.4)	4.72	-5.71 (-6.57 to -4.85)
Rosenstock 2010	73	70	-5.1 (0.5)	-1.6 (0.5)	5.08	-3.50 (-3.66 to -3.34)
Zinman 2009	178	177	-2.0 (4.0)	0.6 (4.0)	4.74	-2.60 (-3.43 to -1.77)
Apovian 2010	96	98	-6.2 (0.5)	-4.0 (0.5)	5.08	-2.19 (-2.34 to -2.04)
Bergenstal 2009	124	124	-1.9 (3.8)	4.1 (5.4)	4.44	-6.00 (-7.16 to -4.84)
Bunck 2009	36	33	-3.6 (3.6)	1.0 (4.6)	3.59	-4.60 (-6.56 to -2.64)
Marre 2009	234	114	-0.2 (0.0)	-0.1 (0.6)	5.08	-0.10 (-0.22 to 0.02)
Nauck 2007	253	248	-2.5 (3.2)	2.9 (3.0)	4.94	-5.40 (-5.94 to -4.86)
Overall; P=0.00					100.00	-2.90 (-3.59 to -2.22)

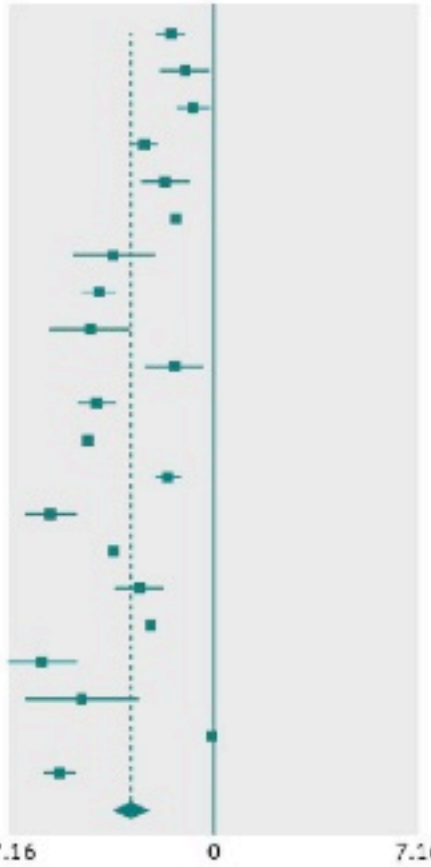


Fig 2 Meta-analysis of change in body weight (kg) in included trials after at least 20 weeks of treatment, using random effects model

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

Trial profile

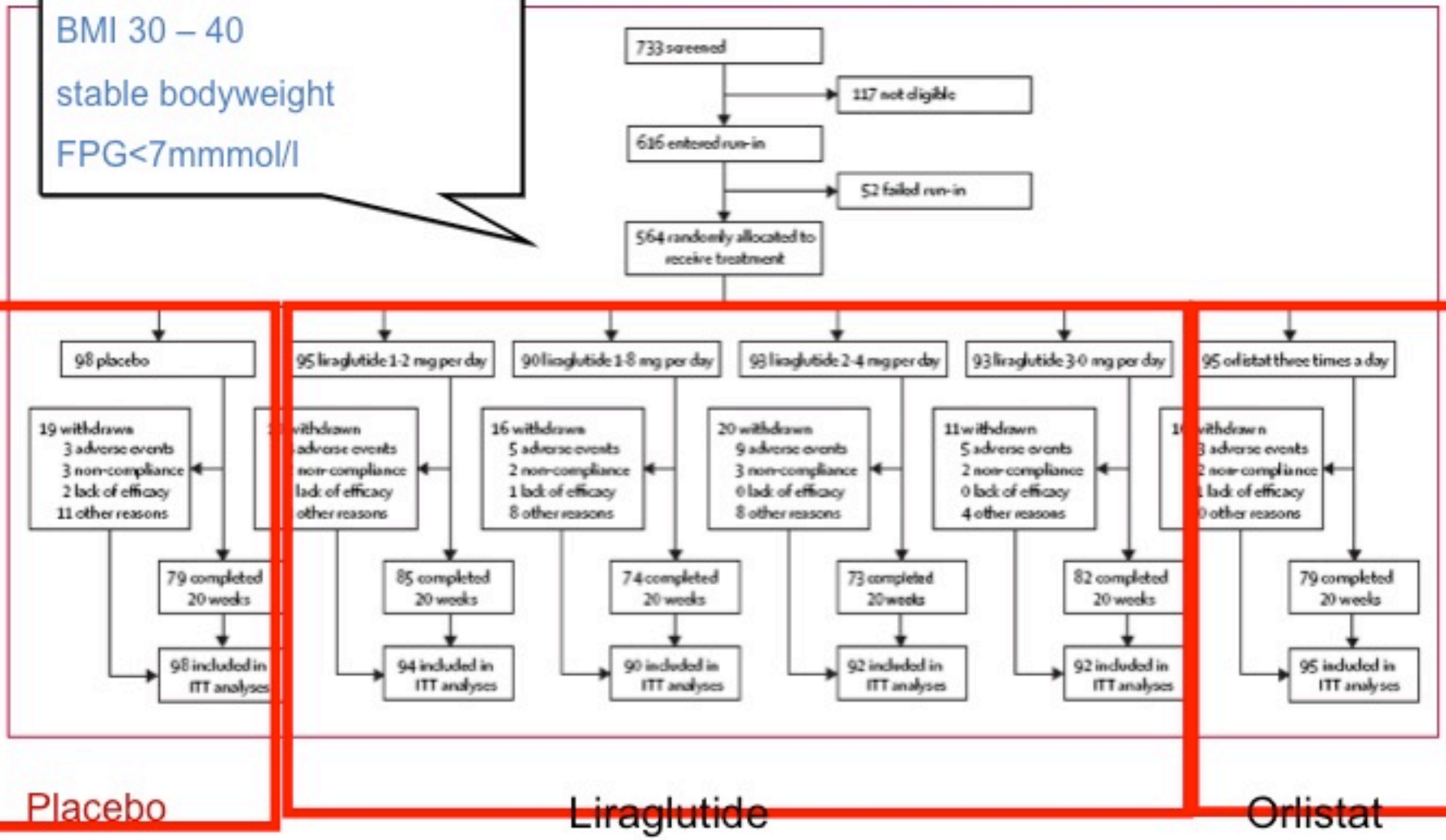
LIRAGLUTIDE

564 patients

BMI 30 – 40

stable bodyweight

FPG<7mmmol/l



Placebo

Liraglutide

Orlistat

LIRAGLUTIDE

Change in bodyweight

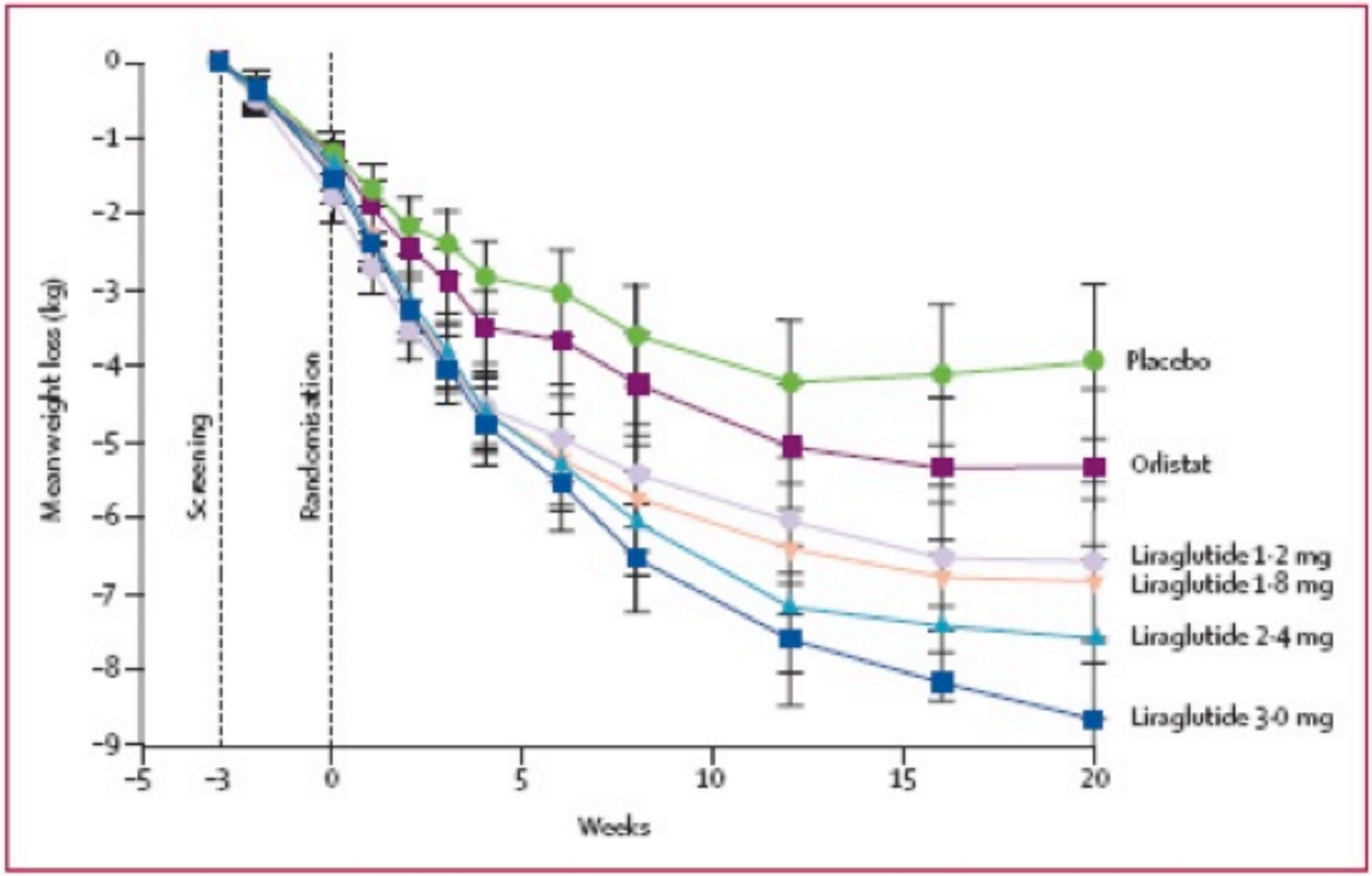


Figure 1: Change in bodyweight Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward.

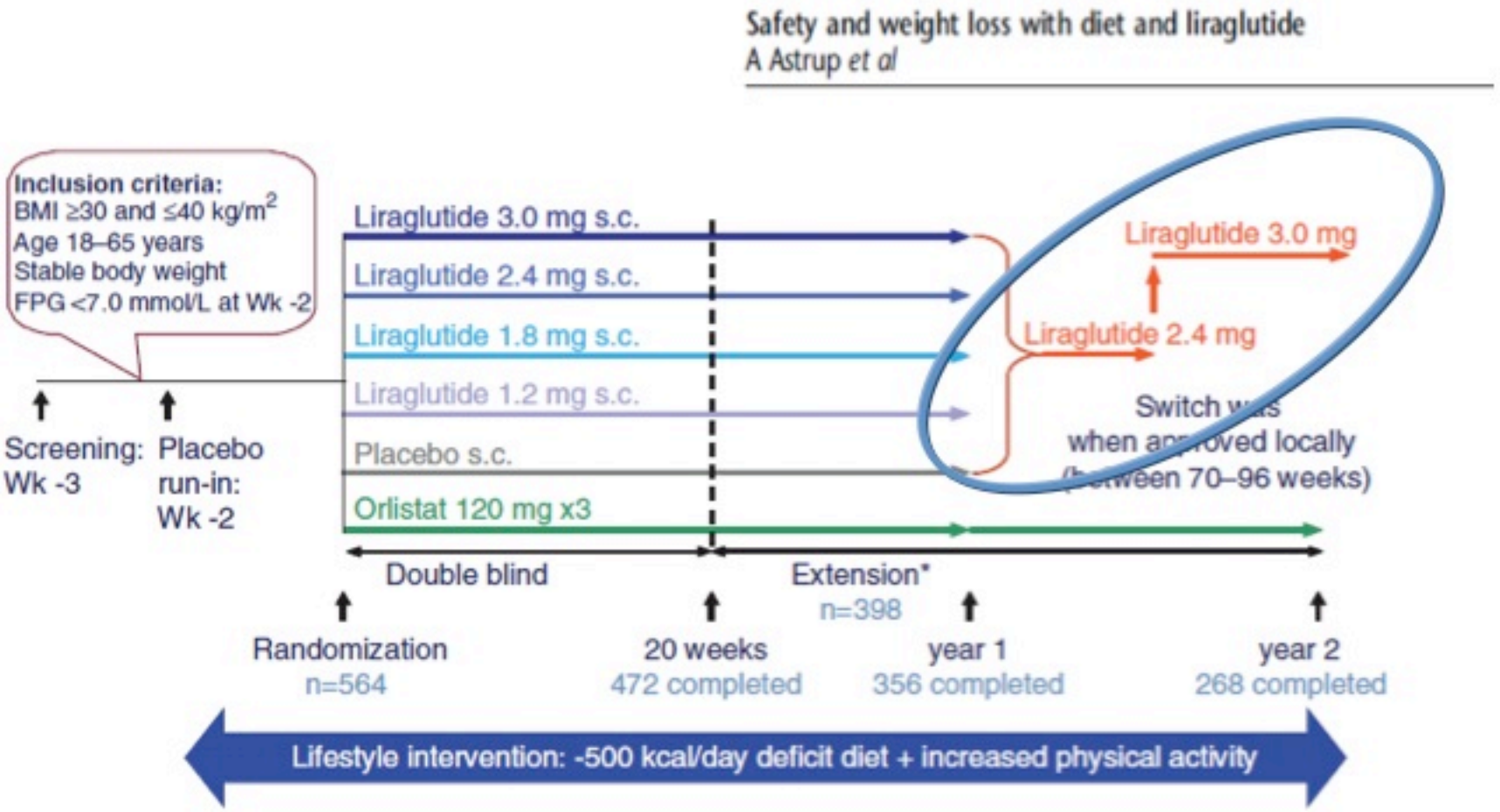
LIRAGLUTIDE

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

Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean ME, Niskanen L, Rasmussen MF, Rissanen A, Rössner S, Savolainen MJ, Van Gaal L.

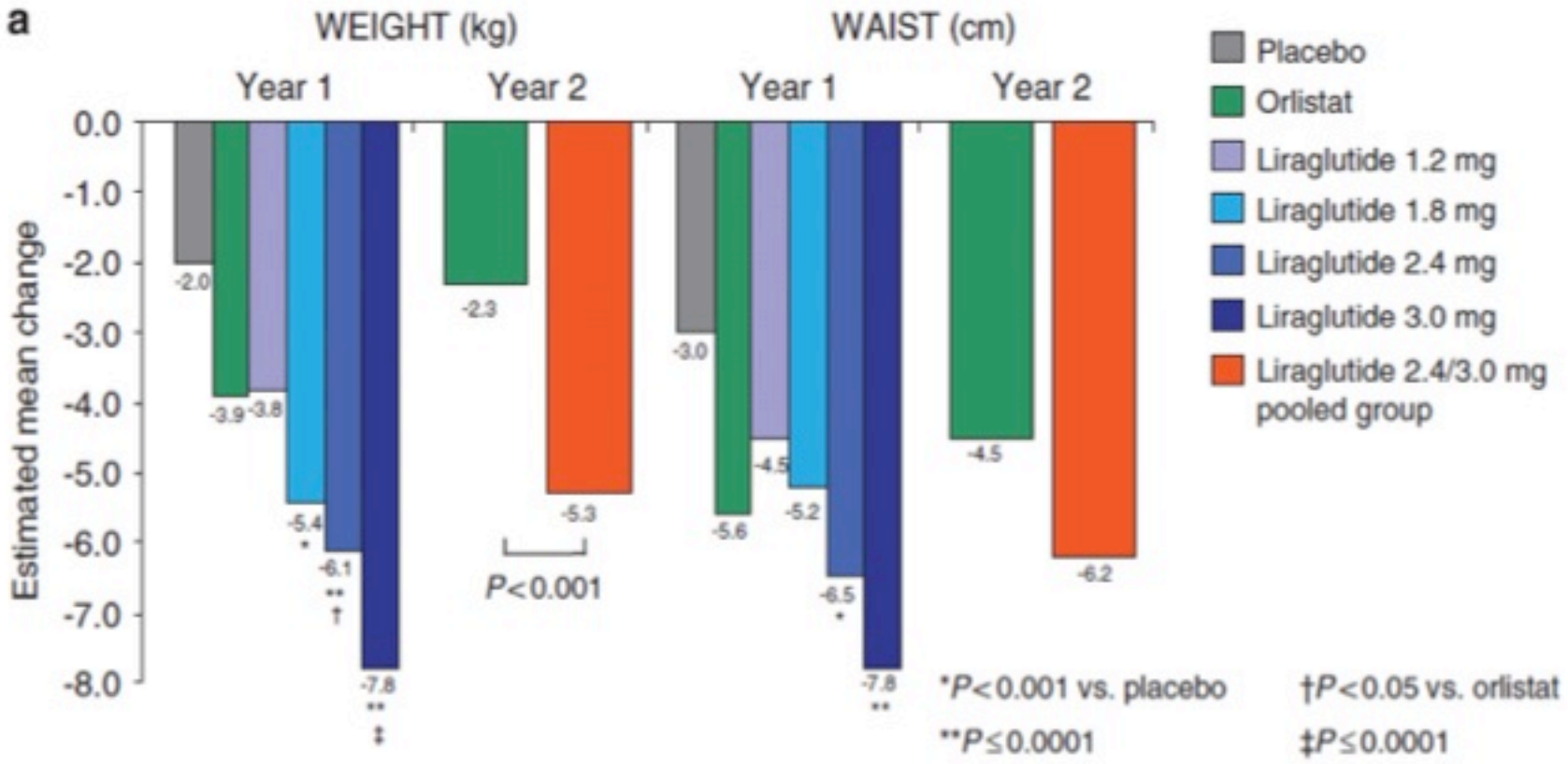
INTERNATIONAL JOURNAL OF OBESITY 2011 1-12 Aug 16.

LIRAGLUTIDE



LIRAGLUTIDE

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



EXENATIDE

Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Subjects With and Without Pre-Diabetes

J. Rosenstock, L. J. Klaff, S. Schwartz, J. Northrup, J. H. Holcombe, K. Wilhelm and M. Trautmann

Diabetes Care. 2010 June; 33(6): 1173–1175.

American Diabetes Association.
Cure • Care • Commitment
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Diabetes Care

EXENATIDE

Exenatide in obese subjects without diabetes

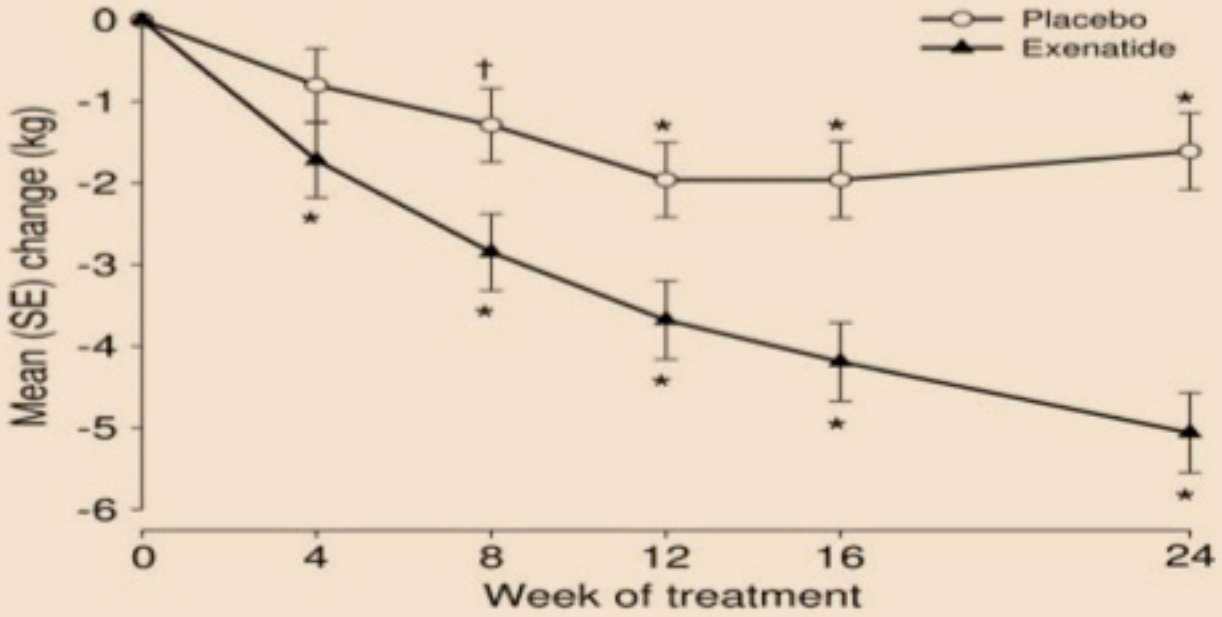
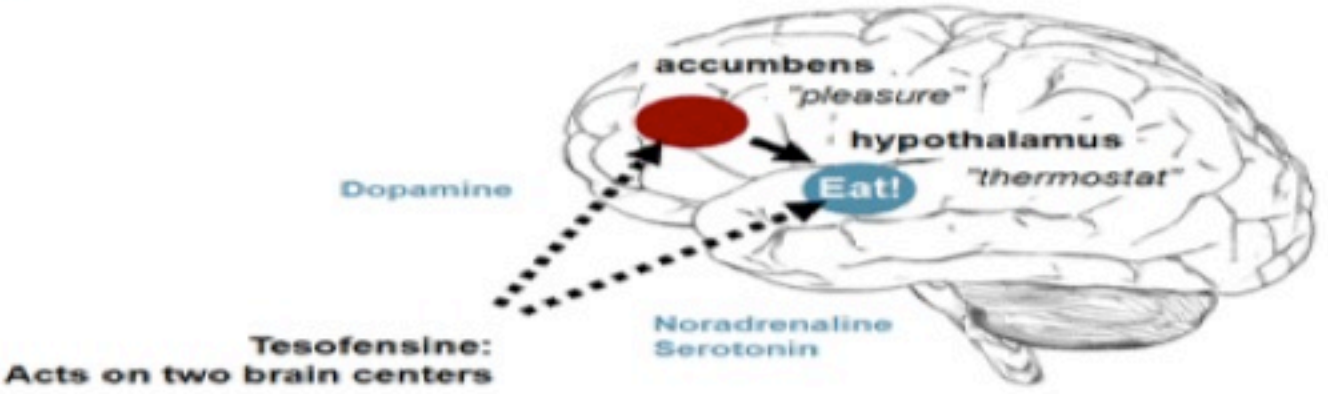


Figure 1—*Changes in body weight over 24 weeks in nondiabetic obese subjects treated with lifestyle intervention and randomized to exenatide or placebo. ○, Placebo (n = 78); ▲, exenatide (n = 73). Results derived from mixed-model repeated-measures analysis and presented as least squares means ± SE. Change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

Tesofensine

Obesity

Tesofensine 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

Background **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**

Published Online October 23, 2008 DOI:10.1016/S0140-6736(08)61525-1

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

TESOFENSINA

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

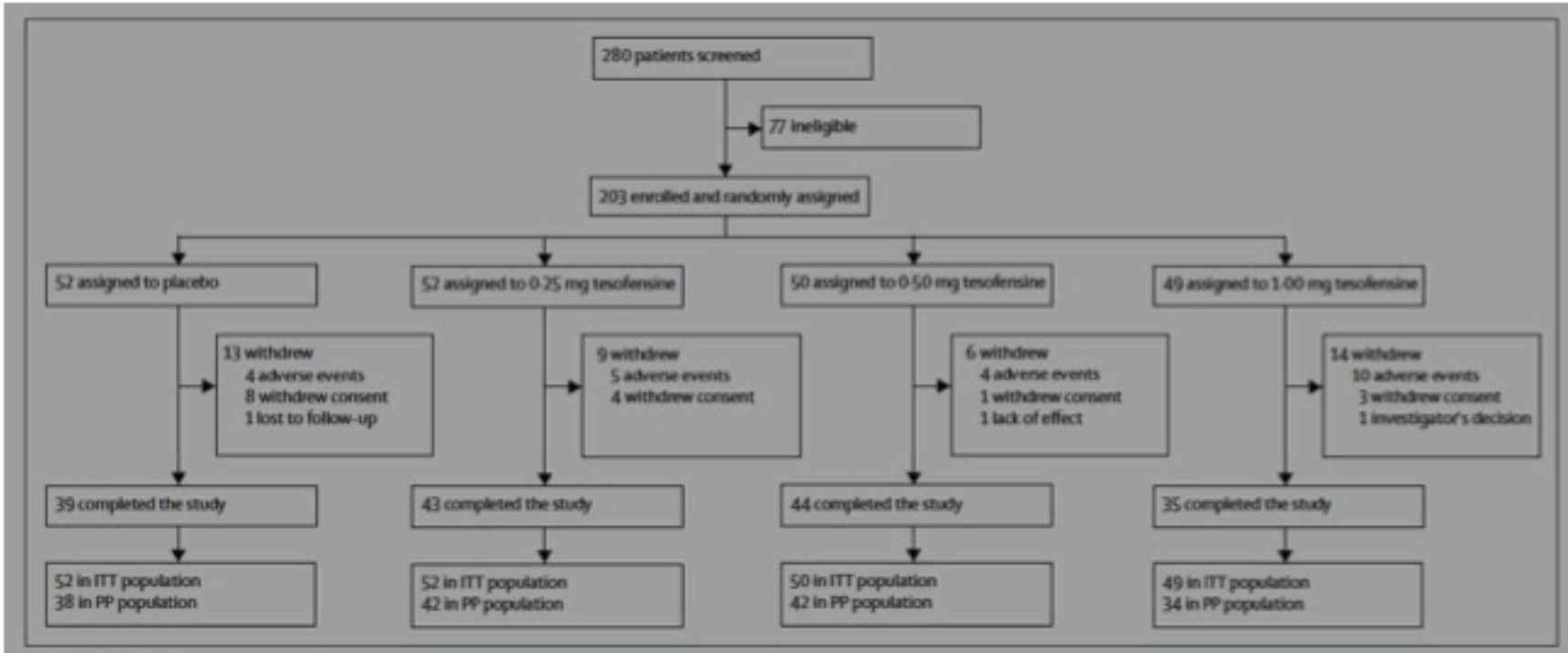
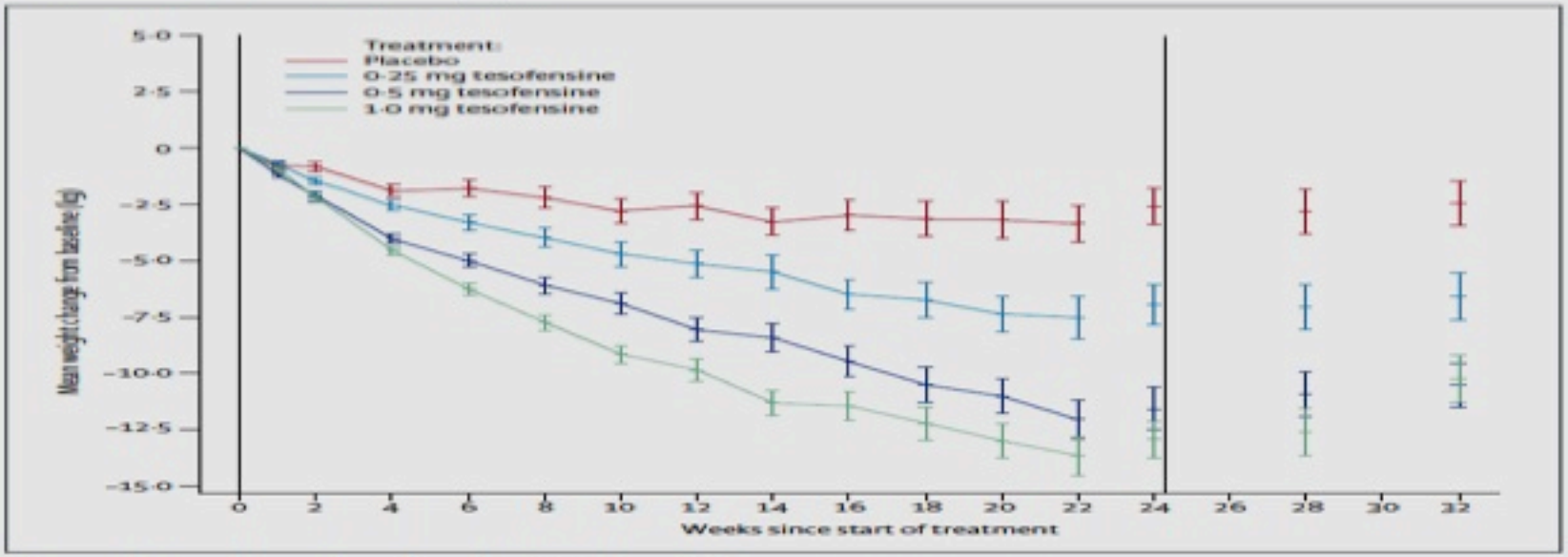


Figure 1: Trial profile

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.



Clinical Therapeutics/Volume 35, Number 1, 2013

New and Emerging Pharmacologic Therapies for Type 2 Diabetes, Dyslipidemia, and Obesity

James R. Taylor, PharmD, CDE[1,2]; Eric Dietrich, PharmD, BCPS[1,2]; and Jason G. Powell, PharmD[1,2]

[1]University of Florida College of Pharmacy, Gainesville, Florida; and [2]Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, Florida

Table V. Comparative Medication Costs.

Medication	WAC Cost, $ (30-Day Supply)[a]
Diabetes	
Metformin 500 mg	10.00
Glyburide 10 mg	15.00
Glipizide XL 20 mg	75.00
Pioglitazone 45 mg	209.27
Exenatide[b] 10 μg	315.25
Liraglutide[c] 1.8 mg	303.34
Sitagliptin[d] 100 mg	223.81
Saxagliptin[e] 5 mg	223.79
Linagliptin[f] 5 mg	223.81
Exenatide (extended release)[g] 2 mg	349.32
Dyslipidemia	
Pravastatin 40 mg	10.20
Lovastatin 40 mg	9.60
Simvastatin 40 mg	11.13
Atorvastatin 40 mg	18.30
Rosuvastatin[h] 40 mg	152.40
Niacin 500 mg	1.44
Niaspan 1000 mg	156.6
Fenofibrate 145 mg	135.00
Omega-3-acid ethyl esters[i] 1 g	184.10
ω3-fish oils 2 g	40.75
Gemfibrozil 600 mg	15.00
Cholestyramine 4 g	18.00
Ezetimibe[j] 10 mg	141.60
Obesity	
Orlistat[k] (orlistat) 120 mg	395.45
Phentermine 37.5 mg	18.60
Diethylpropion IR 25 mg	19.80
Diethylproprion ER 75 mg	25.20
Phendimetrazine IR 35 mg	11.703
Phendimetrazine ER 105 mg	22.20
Phentermine and Topiramate extended-release[l] 15 mg/92 mg	183.90

Table IV. Obesity Clinical Trials Summary.

Drug	Design and Intervention	Results	*P*	Reference
Lorcaserin	R, DB, PC; lor 10 BID, lor 10 QD, or pcb for 52 weeks	At 52 weeks weight loss of >5% of baseline weight occurred in 47.2% of lor 10 BID, 40.2% of lor 10 QD, and in 25% of pcb patients	<0.001 for both doses vs pcb	24
Lorcaserin	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	At 52 weeks weight loss of >5% of baseline weight occurred in 47.5% of lor 10 BID and 20.3% of pcb patients	<0.001	25
Lorcaserin	R, DB, PC; lor 10 BID, lor 10 QD, or pcb for 52 weeks	At 52 weeks weight loss of >5% of baseline weight occurred in 37.5% of lor 10 BID, 44.7% of lor 10 QD, and 16.1% of pcb patients	<0.001 for both doses vs pcb	26
Phentermine-topiramate	R, DB, PC; P/T 15/92, P/T 3.75/23, or pcb for 52 weeks	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	<0.001 for both doses compared to pcb	30
Phentermine-topiramate	R, DB, PC; P/T 7.5 mg/46 mg, P/T 15 mg/92 mg, or pcb for 52 weeks	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	<0.001 for both doses compared to pcb	31
Phentermine-topiramate	R, DB, PC extension of Gadde et al[30]; continued same treatment for 52 weeks	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	<0.001 for both doses vs pcb	32

BID = twice daily; DB = double blind; lor = lorcaserin; PC = placebo controlled; pcb = placebo; P/T = phentermine-topiramate controlled-release; QD = once daily; R = randomized.

Grazie per l'attenzione !