



Late-Breaking Clinical Trial Symposium

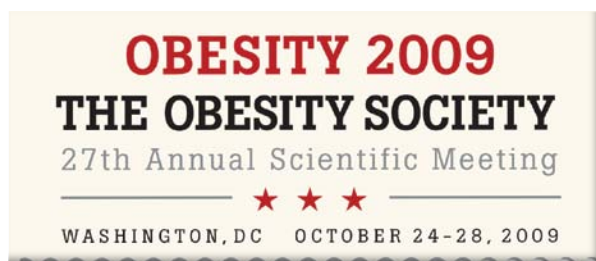
Tuesday, October 27, 2009

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10:00 AM–12:00 PM

10:00 AM–10:20 AM	Paul Sacher	Tackling Child Obesity In The UK: The MEND Program
10:20 AM–10:40 AM	Steven R. Smith, MD	Pramlintide/Metreleptin Combination Treatment For Obesity: Effect of Dose And Baseline BMI on Magnitude of Weight Loss
10:40 AM–11:00 AM	Lee Kaplan, MD	The BLOSSOM Trial: Efficacy and Safety of Lorcaserin in Obese and Overweight Men and Women
11:00 AM–11:20 AM	Frank Greenway, MD	COR-I: A Phase 3 Study Evaluating Two Doses of Naltrexone SR/Bupropion SR Combination Therapy Showed Significant and Sustained Weight Loss in Overweight and Obese Subjects
11:20 AM–11:40 AM	Caroline Apovian, MD	Results of the Phase 3, 56-week, COR-II Study: Naltrexone SR/Bupropion SR Combination Therapy Led to Significant and Sustained Weight Loss in Overweight and Obese Subjects
11:40 AM–12:00 PM	Lars Sjostrom, MD, PhD	Bariatric Surgery And Myocardial Infarction: Effect-Modification of Baseline Fasting Glucose In The Prospective, Controlled Intervention Trial Swedish Obese Subjects



Tackling child obesity in the UK: the MEND Program

Paul Sacher, Paul Chadwick, Maria Kolotourou, Duncan Radley, Tim Cole, Margaret Lawson, Alan Lucas, Atul Singhal

Background: The MEND Program is the largest multi-component child weight management program in the UK¹ (www.mendcentral.org). In this abstract, we present the effects of the MEND intervention beyond the controlled environment of previous clinical trials²⁻⁴. Methods: During 2008, 7-13 year-old overweight or obese children participated in the MEND Program at over 300 locations across the UK. The MEND Program is a 10-week, community and family-based intervention consisting of twice-weekly group sessions including behaviour modification, nutrition education and physical activity. The intervention was delivered by a range of health, exercise, education and social care professionals. Venues included recreation centres, schools and other suitable community spaces. Outcomes were assessed pre- and post-intervention by local Program Leaders who had undergone training. Results: Of the 5699 children (46% boys; mean age 10.5 years; 74% Caucasian, 34% from single-parent families) who participated in the MEND Program from January to December 2008, 3861 (68%) were measured pre and post intervention. Mean BMI and waist circumference z-scores decreased by 0.17 (95%CI: 0.16-0.17; $p < 0.0001$) and 0.21 (95%CI: 0.20-0.22; $p < 0.0001$) respectively. Improvements were also noted in physical activity levels (+3.4 hours per week, $p < 0.0001$), step-test recovery heart rate (-8.4 beats per minute, $p < 0.0001$), self-reported sedentary activities (-6.2 hours per week, $p < 0.0001$), and self-reported body-esteem (+3.6 points, $p < 0.0001$). Mean attendance of the MEND Program sessions was 79% and the drop-out rate was 8%. Conclusion: In accordance with earlier MEND research (feasibility, pilot and randomized controlled trial), attending the MEND Program had beneficial effects on physical outcomes (anthropometry, cardiovascular fitness, physical activity habits) and psychological indices (body image), demonstrating that the program is effective in the short-term, replicable and scalable in community settings.

References: ¹.R. R. Kipping et al., 'Obesity in children. Part 2: Prevention and management', *BMJ*, 337 (2008), a1848. ².P. M. Sacher et al. 'The MEND Programme: effectiveness on health outcomes in obese children', *Obes Rev*, 7 (Suppl.2) (2006), 89. ³.P. M. Sacher et al., 'Assessing the acceptability and feasibility of the MEND Programme in a small group of obese 7-11-year-old children', *J Hum.Nutr Diet.*, 18 (2005), 3-5. ⁴.P. M. Sacher et al., 'Randomized controlled trial of the MEND Program: a family-based community intervention for childhood obesity', *Obesity*, In Press (2009).



Pramlintide/Metreleptin Combination Treatment for Obesity: Effect Of Dose And Baseline BMI On Magnitude Of Weight Loss

Steve R. Smith, Louis J. Aronne, Caroline Apovian, Jean L. Chan, Julie A. Mitchell, Kevin Shan, Nicola Pannacciulli, Stephan Miller, Joy E. Koda, Christian Weyer

Co-administration of amylin, an episodic satiety signal, and leptin, a tonic adiposity signal, elicits synergistic, fat-specific weight loss in diet-induced obese rodents. We previously reported that combination treatment with pramlintide/metreleptin (P/M: 360 μ g/5mg twice daily [BID]), analogs of human amylin and leptin, respectively, elicited more weight loss than either monotherapy in subjects with BMI 27-35 kg/m². Here we assessed several doses of P/M across a broader range of baseline BMI to identify the most effective doses, assess safety, and characterize which patients responded best to P/M treatment. This 28-week, randomized, double-blind, placebo-controlled, phase 2 study compared five P/M doses (180 μ g/2.5mg, 180 μ g/5mg, 360 μ g/1.25mg, 360 μ g/2.5mg, 360 μ g/5mg BID) with placebo and monotherapies (P 360 μ g and M 5mg) in overweight and obese subjects (BMI 27-45 kg/m²) who also participated in a structured lifestyle intervention. Of 608 randomized subjects (70% female; 45 \pm 11 y; BMI 37 \pm 4 kg/m²; 103 \pm 15 kg; mean \pm SD), 360 were deemed evaluable for assessment of the efficacy endpoints. In the evaluable population, all P/M arms achieved greater weight loss at week 28 than the placebo arm (LS mean ~7% vs. 2%, nominal P <0.05). In a prespecified analysis of subjects with BMI \geq 35 kg/m² (N=211) weight loss was similar across P/M and monotherapy arms. In contrast, subjects with BMI <35 kg/m² (N=149) had a dose-dependent reduction in body weight with the P360/M5 dose achieving significantly more weight loss (11.0 \pm 1.7%, LS mean \pm SE) than placebo (1.8 \pm 1.5%) or either monotherapy (P360: 5.1 \pm 1.4%, M5: 4.9 \pm 1.5%; all P <0.05). This weight loss was predominantly due to loss of fat (P360/M5: 8.0 kg fat mass vs 2.2 kg fat-free mass, DEXA). Placebo-corrected weight loss with P360/M5 was more than additive of the corresponding monotherapies (P360/M5: 9.2%, P360: 3.3%, M5: 3.1%) as was placebo-corrected fat loss (P360/M5: 5.7 kg, P360: 1.2 kg, M5: 1.4 kg). The proportion of subjects (BMI <35 kg/m²) achieving \geq 5% and \geq 10% weight loss at week 28 with P360/M5 was 93% and 64%, respectively, compared to 24% and 6% with placebo. Mild to moderate nausea and injection site adverse events were the most common AEs. Importantly, there were no cardiovascular or neuropsychiatric safety signals. These findings confirm and expand our previous clinical results by identifying subjects with a BMI <35 kg/m² as those with the most substantial weight loss response to P/M treatment.



The BLOSSOM Trial: Efficacy and Safety of Lorcaserin in Obese and Overweight Men and Women

Lee M. Kaplan; Steven R. Smith; Neil J. Weissman; Martin Mollen; Dan Streja; Fares Arguello; Leslie Moldaue; Emil Chuang; Christen Anderson; Matilde Sanchez; Meredith Fidler; Brian Raether; William Shanahan, for the BLOSSOM Study Group

Lorcaserin is a selective 5HT_{2C} agonist that induces weight loss without the cardiac valvular effects of non-specific 5HT agonists in preclinical models and in clinical trials completed to date. In a recently completed controlled trial of 3182 patients (BLOOM), 47.5% of patients taking 10 mg lorcaserin BID lost at least 5% of baseline body weight at week 52 compared to 20.3% in the placebo group (ITT). There was no evidence of drug-induced valvulopathy. The BLOSSOM trial was a randomized, double-blind, placebo-controlled study of lorcaserin in 18 to 65 years old patients, who were obese (BMI 30-45 kg/m²), or were overweight (BMI 27-45 kg/m²) with at least one significant comorbid condition. Unlike the BLOOM trial, patients with pre-existing echocardiographic FDA-defined valvulopathy (mild or greater aortic regurgitation, or moderate or greater mitral regurgitation) were enrolled into the BLOSSOM trial. Patients were randomized in a 2:1:2 ratio to receive lorcaserin 10 mg BID, lorcaserin 10 mg QD or placebo for 52 weeks. A lifestyle modification program that included a 600 kcal deficit diet and moderate exercise was administered beginning with the first dose of study medication. The co-primary endpoints of the study were the proportion of subjects who lost at least 5% and 10% of their baseline body weight, and mean weight change at week 52. Secondary endpoints were changes in lipid parameters (TG, cholesterol, LDL and HDL), blood pressure, body composition, and quality of life. Safety endpoints included echocardiographic valvular regurgitation, and rates of depression and suicidal ideation. RESULTS: Lorcaserin met all 3 co-primary efficacy endpoints. 4008 subjects were enrolled into the study. At baseline, mean weight was [mean (sd)] 100.2 (16.02) kg and BMI was 35.9 (4.21) kg/m². The mean age was 43.8 (11.8) years, and 79.8% of participants were female. Race/ethnicity was balanced across treatment groups. Study completion rates were 57.2% and 59% of lorcaserin 10mg BID and 10mg QD treated patients and 52% of the placebo group. At Week 52, weight reduction of 5.8 kg and 4.7 kg was observed in the lorcaserin 10 mg BID and lorcaserin 10 mg QD groups, compared with a placebo response of 2.9 kg ($p < 0.0001$ for each compared to placebo, ITT-LOCF). Patients completing the study according to the protocol lost 7.7, 6.5, and 3.9 kg, respectively ($P < 0.0001$ for both comparisons to placebo). Categorical 5% weight loss (ITT) was achieved in 47.2% of patients in the lorcaserin 10 mg BID group, 40.2% of the lorcaserin 10 mg QD group, and 25% in the placebo group. Categorical 10% weight loss (ITT) was achieved by 22.6%, 17.4% and 9.7% of patients in the lorcaserin 10 mg BID, 10 mg QD and placebo groups, respectively. Headache, fatigue, nausea, and dizziness were the most common adverse events associated with lorcaserin, and each occurred at a placebo adjusted rate of $< 5\%$. The rates of FDA valvulopathy were equal in the lorcaserin 10 mg BID and placebo groups ($p > 0.999$). CONCLUSIONS: Lorcaserin promoted dose-related weight loss in obese and overweight adults. Lorcaserin was well tolerated and was not associated with valvular insufficiency.



COR-I: A Phase 3 Study Evaluating Two Doses of Naltrexone SR/Bupropion SR Combination Therapy Showed Significant and Sustained Weight Loss in Overweight and Obese Subjects

Frank Greenway, Ken Fujioka, Raymond Plodkowski, Maria Guttadauria, Gary Tollefson, Janelle Erickson, Dennis Kim, Eduardo Dunayevich

COR-I is a phase 3, randomized, double-blind, placebo-controlled, 56-week study examining the efficacy and safety of two doses of naltrexone sustained release (SR)/bupropion SR for the treatment of obesity. Subjects (N=1742) were randomized 1:1:1 to receive oral NB32 (32 mg naltrexone/360 mg bupropion daily), NB16 (16 mg naltrexone/360 mg bupropion daily) or placebo (PBO). Primary endpoints were the percent change from baseline in body weight and the proportion of subjects with $\geq 5\%$ weight loss at Week 56 (ITT-LOCF; subjects with ≥ 1 post-baseline weight measurement on study drug; NB32 N=471, NB16 N=471, PBO N=511). Additional endpoints included the proportion of subjects achieving $\geq 10\%$ and $\geq 15\%$ weight loss, change in waist circumference (WC), lipids, quality of life (QOL), and control of eating at Week 56. Baseline characteristics were similar between groups (mean: age 44 y, 85% female, 75% Caucasian, weight 100 kg, BMI 36.2 kg/m², WC 109 cm, triglycerides (TG) 129 mg/dL, HDL 52 mg/dL, LDL 120 mg/dL). Completion rates were 51% NB32, 49% NB16 and 50% PBO. Week 56 weight loss was significantly greater ($P < 0.001$) with NB32 (-6.1%) and NB16 (-5.0%) vs. PBO (-1.3%). Significantly more ($P < 0.001$) NB32- and NB16-treated vs. PBO-treated subjects achieved categorical weight loss of $\geq 5\%$ (48% and 39% vs. 16%), $\geq 10\%$ (25% and 20% vs. 7%), and $\geq 15\%$ (12% and 9% vs. 2%). NB32 and NB16 were associated with greater improvements vs. PBO in: WC (-6.2 cm [$P < 0.001$] and -5.0 cm [$P < 0.001$] vs. -2.5 cm), HDL (+3.4 mg/dL [$P < 0.001$] and +3.4 mg/dL [$P < 0.001$] vs. -0.1 mg/dL), and TG (-18.1 mg/dL [$P < 0.001$] and -9.3 mg/dL [NS] vs. -3.5 mg/dL). The change in LDL did not reach statistical significance (-4.4 and -3.7 mg/dL vs. -3.3 mg/dL). NB32 and NB16 were also associated with improvements in QOL and control of eating. The most frequent adverse events were (for NB32 and NB16 vs. PBO) nausea (29.8% and 27.2% vs. 5.3%), headache (13.8% and 16.0% vs. 9.3%), and constipation (15.7% and 15.8% vs. 5.6%). Nausea was mostly mild to moderate in severity, transient, and occurred early in the trial. NB32 and NB16 were not associated with increased adverse event rates for depression or suicidal ideation. The frequency of serious adverse events was similar for NB vs. PBO. In summary, NB was generally well tolerated and was associated with clinically significant, dose dependent and sustained weight loss, in addition to reduced waist circumference, improvements in HDL, triglycerides, and quality of life.



Results of the Phase 3, 56-week, COR-II Study: Naltrexone SR/Bupropion SR Combination Therapy Led to Significant and Sustained Weight Loss in Overweight and Obese Subjects

Caroline Apovian, Louis Aronne, Holly Wyatt, Domenica Rubino, Amy Rosen, Dennis Kim, Eduardo Dunayevich

COR-II is a phase 3, double-blind, placebo-controlled, 56-week study examining the efficacy and safety of naltrexone sustained-release (SR)/bupropion SR in overweight and obese subjects. Subjects (N=1496) were randomized 2:1 to oral NB32 (32 mg naltrexone/360 mg bupropion daily) or placebo (PBO). Between Weeks 28 and 44 inclusive, NB32-treated subjects with <5% weight loss were blindly re-randomized (1:1, N=251) to receive NB32 or NB48 (48 mg naltrexone/360 mg bupropion daily) for the remainder of the study. Primary endpoints were the % change from baseline in body weight and the % of subjects with $\geq 5\%$ weight loss at Week 28 (ITT-LOCF; subjects with ≥ 1 post-baseline weight measurement on study drug; NB32 N=825, PBO N=456). These endpoints were also examined at Week 56. The % of subjects with $\geq 10\%$ and $\geq 15\%$ weight loss and the change from baseline in waist circumference, triglycerides, HDL and LDL were also examined. As pre-specified, NB48-treated subjects were excluded from Week 56 efficacy analyses and subjects re-randomized to NB32 were double-weighted. Baseline characteristics were similar between groups (mean: age 44 y, 85% female, 84% Caucasian, weight 100 kg, BMI 36 kg/m², waist circumference 109 cm, triglycerides (TG) 130 mg/dL, HDL 52 mg/dL, LDL 120 mg/dL). Study completion rates were 54% for both groups. Week 28 weight loss was -6.5% NB32 vs. -1.9% PBO (P<0.001), and more NB32-treated subjects achieved $\geq 5\%$ (55.6% vs. 17.5%), $\geq 10\%$ (27.3% vs. 7.0%) and $\geq 15\%$ weight loss (10.2% vs. 1.8%)(all P<0.001). Week 56 weight loss was -6.4% NB32 vs. -1.2% PBO (P<0.001), and more NB32-treated subjects achieved $\geq 5\%$ (56.3% vs. 17.1%), $\geq 10\%$ (32.9% vs. 5.7%), and $\geq 15\%$ weight loss (15.7% vs. 2.4%)(all P<0.001). In exploratory analyses, NB32-treated subjects had improved markers of cardiovascular risk vs. PBO at Week 56: waist circumference, -6.7 cm vs. -2.1 cm (P<0.001); TG, -11.8 mg/dL vs. -0.5 mg/dL (P<0.01); HDL, +3.6 mg/dL vs. -0.9 mg/dL (P<0.001); LDL, -6.2 mg/dL vs. -2.1 mg/dL (P<0.01). The most frequent adverse events were nausea (29.2% NB vs. 6.9% PBO), constipation (19.1% vs. 7.1%), and headache (17.5% vs. 8.7%). Nausea was mostly mild/moderate in severity, transient and occurred early. Treatment with NB was not associated with increases in depression or suicidal ideation adverse events. The frequency of serious adverse events was similar for NB vs. PBO. In conclusion, NB therapy was generally well-tolerated and generated sustained, meaningful weight loss.



Bariatric surgery and myocardial infarction: effect-modification of baseline fasting glucose in the prospective, controlled intervention trial Swedish Obese Subjects

Lars Sjostrom, Peter Jacobson, Markku Peltonen, Kristjan Karason, Kristina Narbro, C David Sjostrom, Lena Ms Carlsson

Background: Obesity is a risk factor for myocardial infarction (MI). The Swedish Obese Subjects (SOS) study is the first intervention trial in the obese population to provide prospective controlled incidence data on MI. Methods: 2010 obese patients underwent bariatric surgery and 2037 contemporaneously matched obese controls received conventional obesity treatment. A randomized design was not approved for ethical reasons. Inclusion criteria of this multi-center study were age 37 to 60 years and a BMI of 34 kg/m² or more for men and 38 kg/m² for women. While overall mortality (published in 2007) was the primary endpoint, fatal plus non-fatal MI was a predefined secondary endpoint. Results: Patients were included between 1987 and 2001. At matching, BMI was 41.8±4.4 kg/m² (Mean±SD) in the surgery group and 40.9±4.3 kg/m² in the control group. Age was 46.1±5.8 and 47.4±6.1 years, respectively. Twenty-nine percent were men in both study arms. The median follow up time until date of analysis (Dec. 31, 2007) was 12.8 years (range 0 to 20.1 years). After 1, 2, 10 and 15 years, body weight had changed -30.3, -28.5, -19.9 and -20.8 kg from baseline in the surgery group, and -0.9, -0.1, +1.3 and -1.8 kg in the control group, respectively (p<0.001 at all observation times). Compared to all obese controls, the unadjusted cumulative incidence of fatal plus non-fatal MI was not different in the surgery patients at the end of the observation period (104 MI cases in surgery group and 113 in the control group, HR=0.90, 95% CI 0.69 to 1.18, p=0.445). The cumulative incidence curves of the two study groups seemed to be maximally separated in favor of surgery after 11 study years, but converged thereafter and crossed each other after 18 study years. There was a significant treatment-low/high glucose interaction with respect to MI (p=0.007). For subjects with fasting *blood* glucose over or equal to the median value (4.72 mmol/L) at baseline, surgery was associated with a favorable effect on the incidence of MI (61 vs. 78 MI cases, respectively, HR=0.66, 95% CI 0.47 to 0.92, p=0.014) while in subjects with blood glucose below the median, surgery was not an advantage (43 vs. 35 cases, HR=1.40, 95% CI 0.90 to 2.19, p=0.14). Interpretation: There was no overall effect of bariatric surgery on MI over up to 20 study years but a significant effect of surgery on MI in subjects with baseline glucose values above the median.