DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

BACKGROUND MEMORANDUM

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To:	Members and Consultants, Endocrinologic and Metabolic Drugs Advisory Committee March 28-29, 2012
Topic:	The role of cardiovascular assessment in the pre- and post-approval settings for drugs developed for the treatment of obesity

DISCLAIMER

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I. Introduction

Drugs approved by the Food and Drug Administration (FDA) for the long-term management of obesity, including weight loss and maintenance of weight loss, should be used in conjunction with a reduced-calorie diet and are recommended for patients with an initial body mass index ≥ 30 kg/m^2, or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension). FDA evaluates drugs for the management of obesity based primarily on changes in body weight.

According to the 2007 FDA draft guidance for industry entitled "Developing Products for Weight Management," demonstration of efficacy after 1 year of treatment can be achieved by meeting *either* of the following co-primary endpoints:

- The difference in mean weight change (expressed as a percentage change relative to baseline) between the active-treatment group and placebo is $\geq 5\%$ and the difference is statistically significant.
- The proportion of patients who lose $\geq 5\%$ of their baseline body weight in the active-treatment group is at least 35%, is approximately double the proportion in the placebo group, and the difference in proportions between the active and placebo groups is statistically significant.

Epidemiologic data indicate that relatively small amounts of diet- and/or exercise-induced weight loss, if maintained, are associated with favorable changes in biomarkers of cardiovascular (CV) risk. The guidance benchmark of a mean 5% weight loss is based on data demonstrating that 5 to 10% weight loss is associated with favorable changes in cardiometabolic biomarkers, such as increases in HDL-C, reductions in blood pressure and improvements in measures of glycemia.[1,2] Therefore, it has been hypothesized that drug therapy resulting in weight loss will reduce major cardiac events. However, this hypothesis has only been adequately tested with one weight loss-drug, sibutramine. The results of the Sibutramine Cardiovascular Outcomes Trial (SCOUT) showed that sibutramine compared to placebo increased rather than decreased the relative risk for major adverse cardiac events (MACE) in a population of older overweight and obese at-risk individuals. The data from SCOUT, together with sibutramine's efficacy data, led the Agency to conclude that the benefits of the drug did not outweigh its risks. Sibutramine was withdrawn from the market in October 2010.

In July 2008, FDA held an advisory committee meeting to discuss the role of CV assessment in the pre-approval and post-approval settings for drugs developed for the treatment of type 2 diabetes mellitus. Subsequently, FDA published a guidance for industry entitled, *Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.*[3]

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1 Poirier P et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Circulation.* 2006;113:898-918.
2 Knowler WC et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *NEJM.* 2002;346:393-403.
3 Guidance for industry: Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to

The guidance for developing new drugs for the treatment of type 2 diabetes recommends that:

- Pharmaceutical companies show that their therapies do not result in an unacceptable increase in CV risk. This recommendation applies even for those products that do not have a signal of CV harm in non-clinical or clinical studies.
- Pharmaceutical companies establish an independent CV endpoint committee to prospectively and blindly adjudicate MACE during phase 2 and 3 clinical trials.
- Phase 2 and 3 clinical trials be designed so that a pre-specified meta-analysis of MACE can be reliably performed.
- Phase 3 trials enroll patients at increased CV risk, such as elderly patients and those with renal impairment.
- Trials be of sufficient duration to capture an adequate number of CV events and obtain long-term safety data.
- Pharmaceutical companies provide evidence ruling out an upper threshold of excess CV risk with the investigational drug vs. control.

Thus, the SCOUT results, as well as our experience with other products to treat obesity and diabetes, have prompted FDA to ask whether long-term CV trials should be part of the approval process for drug developed for the treatment of obesity.

The purpose of this briefing document is to provide introductory material to orient advisory committee members and guest experts for the formal presentations and ensuing discussion on March 28th and 29th, 2012.

During the first day of the advisory committee meeting, experts in the field of obesity, diabetes, cardiology and statistics will present background information that will lay the foundation for discussion among panel members and the speakers (Table 1). Most of the second day of the advisory committee meeting will be reserved for an extensive discussion among the advisory committee members.

Table 1. Topics to be Presented to the Advisory Committee Panel

FDA's 2007 guidance for obesity drug development
Who uses obesity drugs?
The morbidity of obesity and the benefits of weight loss: a focus on non-CV effects
Obesity and CV disease: epidemiology and pathophysiology
Obesity and the effect of weight loss on CV disease (lifestyle, drug, bariatric surgery)
The Look AHEAD (Action for Health in Diabetes) trial: a lifestyle intervention trial of weight loss for the prevention of CV disease in type 2 diabetes
Sibutramine and SCOUT; rimonabant and CRESCENDO
FDA's 2008 guidance for the evaluation of CV risk for antidiabetic therapies: rationale and key features

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treat type 2 diabetes. In: Guidances (drugs). United States Food and Drug Administration. 2008. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/ucm071627.pdf. Accessed 13 Jan 2012.

| FDA's 2008 guidance for the evaluation of CV risk for antidiabetic therapies: experience to date and lessons learned |
| Unique challenges of CV outcome trials with obesity drugs |

This FDA-prepared document contains:
- Background information on the epidemiology and health risks associated with obesity
- FDA's current approach to the approval of drugs developed for the treatment of obesity
- A summary of CV trials conducted with obesity drugs
- A summary of the CV assessment of drugs for the treatment of type 2 diabetes mellitus
- Issues relating to CV assessment of drugs developed for the treatment of obesity
- Points for discussion for use during the advisory committee panel's deliberations
- Appendices with pertinent references

II. Obesity

Obesity is currently defined as a body mass index (BMI) of 30 kg/m^2 or greater, and a BMI between 25 and 29.9 kg/m^2 is termed overweight. In 2010, the International Obesity Task Force estimated that approximately 1.0 billion adults are currently overweight and a further 475 million individuals worldwide are obese.[4]

According to 2009-2010 data from the National Health and Nutrition Examination Survey (NHANES), among US adults, the age-adjusted obesity prevalence is 35.7%. Non-Hispanic black men and women have the highest obesity prevalence rates: 38.8% for men and 58.5% for women. Grade 2 obesity (BMI >35 kg/m^2) and grade 3 (BMI >40 kg/m^2) showed the highest rates for non-Hispanic blacks: 20.0% for non-Hispanic black men and 30.7% for non-Hispanic black women.

Over the 12-year period from 1999 through 2010, the prevalence of obesity showed no significant increase among women overall, but increases were significant for non-Hispanic black women and Mexican-American women. For men, there was a significant linear trend over the 12-year period. For both men and women, the prevalence of obesity during 2009-2010 did not differ significantly from the prevalence during 2003-2008.[5]

Between 2009 and 2010, 17% of U.S. children and adolescents were obese (BMI ≥ 95th percentile), with 32% either overweight or obese (BMI ≥ 85th percentile).[6] The

4 International Obesity Taskforce. assessed 12 Jan 2012
<http://www.iaso.org/iotf/obesity/obesitytheglobalepidemic/>
5 Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among us adults, 1999-2010. JAMA 2012; DOI:10.1001/jama.2012.39. Available at: http://jama.ama-assn.org.
6 Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among us children and adolescents, 1999-2010. JAMA 2012; DOI:10.1001/jama.2012.40. Available at: http://jama.ama-assn.org.

prevalence of obesity among male children and adolescents aged 2 through 19 years (19%) was significantly higher than among female children and adolescents (15%). Racial differences were also seen with black children and adolescents having a prevalence of obesity of 24% compared with 21% for Hispanics and 14% for whites.

Obesity increases the risk of premature death and comorbid conditions such as type 2 diabetes, hypertension, dyslipidemia, CV disease, osteoarthritis of the knee, sleep apnea, and certain cancers.[7,8,9,10] The relationships between BMI and risks for death and major comorbidities vary by age, gender, race, and smoking status, but, in general, are lowest in individuals with BMIs of 18.5 kg/m^2 to 24.9 kg/m^2 and increase in a curvilinear or linear manner between BMIs of 25 kg/m^2 to approximately 40 kg/m^2. Grade 2 obesity (BMI >35 kg/m^2) is associated with excess mortality, primarily from CV disease, diabetes, and certain cancers.[11,12,13] Furthermore, an increased level of visceral or intra-abdominal adiposity, independent of BMI, has been associated with increases in the risk for metabolic derangements and perhaps CV disease.[14,15,16]

In overweight and obese individuals, particularly individuals with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes, long-term weight loss of 5 to 10% following diet, exercise, and in some cases, drug treatment, is associated with improvement in various metabolic and CV risk factors.[17,18,19]

III. Pharmacologic Treatments for Obesity

In the early 1970s, due to concerns about transient efficacy and the potential for physical dependency, FDA restricted the indication of obesity drugs, including amphetamine and

7 Li A et al. Meta-Analysis: Pharmacologic Treatment of Obesity. Ann Intern Med. 2005;142:532-546.
8 Caterson, ID, V Hubbard, GA Bray, R Grunstein, BC Hansen et al., 2004, Obesity, A Worldwide Epidemic Related to Heart Disease and Stoke, Circulation, 110:e476-e483.
9 Calle, EE, MJ Thun, JM Petrelli, C Rodriquez, and CW Heath, 1999, Body Mass Index and Mortality in a Prospective Cohort of U.S. Adults, New England Journal of Medicine, 341:1097-1105.
10 Malnick SD, Knobler H. The medical complications of obesity. QJM. 2006;99(9):565–579.
11 Malnick SD, Knobler H. The medical complications of obesity. QJM. 2006;99(9):565–579.
12 Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007;298(17):2028–2037.
13 Orpana HM, Berthelot JM, Kaplan MS, Feeny DH, McFarland B, Ross NA. BMI and mortality: results from a national longitudinal study of Canadian adults. Obesity. 2010;18:214-218.
14 Janssen, I, PT Katzmarzyk, and R Ross, 2004, Waist Circumference and not Body Mass Index Explains Obesity-Related Health Risk, American Journal of Clinical Nutrition, 79:379-384.
15 Rexrode, KM, VJ Carey, CH Hennekens, EE Walters, GA Colditz et al., 1998, Abdominal Obesity and Coronary Heart Disease in Women, Journal of the American Medical Association, 280:1843-1848.
16 Zhu, S, Z Wang, S Heshka, M Heo, MS Faith et al., 2002, Waist Circumference and Obesity-Associated Risk Factors Among Whites in the Third National Health and Nutrition Examination Survey: Clinical Action Thresholds, American Journal of Clinical Nutrition, 76:743-749.
17 Douketis, JD, C Macie, L Thabane, and DF Williamson, 2005, Systematic Review of Long-Term Weight Loss Studies in Obese Adults: Clinical Significance and Applicability to Clinical Practice, International Journal of Obesity, 29:1153-1167.
18 Poirier P et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. Circulation. 2006;113:898-918.
19 Knowler WC et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. NEJM. 2002;346:393-403.

related congeners such as phentermine, to the short-term (a few weeks) treatment of obesity (Table 2).

Since the 1990s, a key consideration when evaluating obesity drugs is understanding that overweight and obesity are chronic conditions; hence, the successful treatment of these conditions requires chronic therapy. FDA's position – which is consistent with the NIH guidelines for treatment of obesity[20] – has been that any drug developed for obesity should not only be effective, but should demonstrate safety for long-term or chronic use in a large, diverse population.

Following removal from the market of dexfenfluramine for valvulopathy in 1997 and sibutramine for adverse CV effects in 2010, orlistat is currently the only obesity drug approved for long-term use in the United States (Table 2). Other notable market withdrawals have included ephedrine-containing dietary supplements for adverse CV effects in 2004 and phenylpropanolamine-containing weight control products for hemorrhagic stroke in 2000.

Table 2. FDA-Approved Medications for the Treatment of Obesity

Drug Trade name/ Generic name	Approval Date	Mechanism of Action/Daily dose range (mg)	Indication
Short-Term Treatment of Obesity			
ADIPEX-P and Generic/Phentermine hydrochloride	1959	Norepinephrine reuptake inhibitor (sympathomimetic) 15-37.5 mg/day	Indicated as a short-term (a few weeks) adjunct 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 BMI $\geq$30 kg/m^2, or $\geq$27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia).
TENUATE and Generic/ Diethylpropion	1959	Norepinephrine releasers; similar in chemical structure to bupropion (sympathomimetic) 75 mg/day	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial BMI of 30 kg/m^2 or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone
BONTRIL; BONTRIL PDM; and generic/ Phendimetrazine	1959	Norepinephrine releasers; chemically related to amphetamines and is a Schedule III drug (sympathomimetic) 70-210 mg/day	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial BMI of 30 kg/m^2 or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone
DIDREX and Generic/ Benzphetamine	1960	Norepinephrine releasers (sympathomimetic)	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial BMI of 30 kg/m^2 or higher who have not responded to appropriate

20 Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NIH Publication Number 98-4083; September 1998. (Practical Guide. NIH Publication Number 00-4084; October 2000) U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute

Drug Trade name/ Generic name	Approval Date	Mechanism of Action/Daily dose range (mg)	Indication
		25-150 mg/day	weight reducing regimen (diet and/or exercise) alone
Chronic Treatment of Obesity			
XENICAL/orlistat NDA 20766	1999	Lipase inhibitor 120 mg TID	XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).
Source: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm			

The weight-loss efficacy of obesity medications reviewed by FDA since the late 1990s is shown in Table 3.

Table 3. Mean Percent Weight Loss at One Year for Various Obesity Drugs

	Active LS Mean Weight Loss from Baseline	Placebo LS Mean Weight Loss from Baseline	Treatment Comparison, LS Mean Difference from Placebo	Data Source
Orlistat 120 mg TID Study NM14161	-4.1%	-0.3%	-3.8%	NDA 21887, pg 324/1014
Sibutramine 15 mg QD	-6.4 kg (mean weight change at 1 year)	-1.6 kg (mean weight change at 1 year)	-4.8 kg	Meridia prescribing information

Rimonabant 20 mg QD
  RIO-North American
  RIO-Europe
  RIO-Lipids
  RIO-Diabetes
	-6.5%
	-6.9%
	-7.4%
	-5.5%
		-1.7%
		-2.1%
		-1.9%
		-1.6%
			-4.7%
			-4.7%
			-5.4%
			-3.9%
				NDA 21888, statistical review

Qnexa (phentermine/ topiramate) 15/92 mg QD
  OB-302 (No DM)
  OB-303 (16% DM)
	-10.9%
	-9.8%
		-1.6%
		-1.2%
			-9.4%
			-8.6%
				NDA 22580, FDA Briefing Package, EMDAC meeting, 15 July 2010;NDA 22580 CSR OB-302 Table S1 and CSR OB-303 Table S1

Lorcaserin 10 mg BID
  APD356-009 (No DM)
  APD356-011 (No DM)
	-5.9%
	-5.8%
		-2.2%
		-2.8%
			-3.7%
			-3.0%
				NDA 22529, Summary of Clinical Efficacy, Table 12 NDA 22529, ISE Table 13

NB32 (naltrexone 32 mg/bupropion 360 mg) QD
  NB-301 (No DM)
  NB-302 (No DM)
  NB-304 (DM)
	-6.1%
	-9.3%
	-5.0%
		-1.3%
		-5.1%
		-1.8%
			-4.8%
			-4.2%
			-3.3%
				NDA 200063, ISE Table 18

IV. Approval Process for Drugs for the Treatment of Obesity

In 2007, after an advisory committee convened in 2004 to revise FDA's 1996 draft obesity drug guidance, the Division issued a draft guidance entitled "*Developing*

Products for Weight Management". The draft guidance describes the clinical assessment required for the development of obesity drugs for Phase 1, 2, and 3 trials. The pertinent information relevant to the March 28th and 29th advisory committee meeting is summarized below. Please refer to the draft guidance in the Appendix for additional information.

Phase 1 and 2 Development Program
One of the goals of this phase of development is to characterize the pharmacokinetics and dose-response profiles of the new weight-management product in patients with a broad range of BMIs (e.g., 27 kg/m^2 to 35 kg/m^2). Another goal is to identify the most appropriate dose or doses for the pivotal Phase 3 trial. Trials should be designed to differentiate the efficacy of all the active doses versus placebo.

Phase 3 Development Program

Trial Design and Patient Populations
The trials examining the efficacy and safety of obesity drugs should be randomized, double-blind, and placebo-controlled and should include lifestyle modification programs for all patients. Patients should have or be at significant risk for weight-related morbidity and mortality. Such patients include those with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 in the presence of comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea, CV disease). The trials should include a representative sample of patients from the various demographic, ethnic, and racial groups in which the prevalence of obesity is highest. Development programs also should include a representative sample of patients with extreme obesity (BMI greater than 40 kg/m^2). Compared with nondiabetic patients, overweight and obese patients with type 2 diabetes often respond less favorably to weight-management products and may face unique safety issues. Therefore, a trial dedicated to patients with type 2 diabetes is strongly encouraged.

Trial Size and Duration
A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment. This sample size, for example, will provide 80% power to rule out with 95% confidence an approximately 50% increase in the incidence of an adverse event that occurs at a rate of 3% per year in the placebo group.

Efficacy Assessment
The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight. Demonstration of efficacy after 1 year of treatment can be achieved by meeting *either* of the following co-primary endpoints:

- Mean: The difference in mean weight loss between the active-treatment group and placebo is $\geq 5\%$ and the difference is statistically significant.

- Categorical: The proportion of patients who lose ≥5% of their baseline body weight in the active-treatment group is at least 35%, is approximately double the proportion in the placebo group, and the difference between the active and placebo groups is statistically significant.

Secondary efficacy endpoints should include, at a minimum, changes in the blood pressure and pulse, lipoprotein lipids, fasting glucose and insulin, HbA1c (in type 2 diabetics), waist circumference, quality of life, and the proportion of subjects who have a meaningful dose-reduction or complete withdrawal of their concomitant medication for the treatment of blood pressure, lipids, or glycemia.

Safety Assessment
In addition to routine safety monitoring, some development programs will require specialized safety assessments. For example, products that directly interact with the 5HT receptor system, specifically the $5HT_2$-receptor subtypes, should include an evaluation of risk for cardiac valvulopathy using serial echocardiography. The development plans for centrally acting weight-management products should include validated assessments of neuropsychiatric function as well as preclinical and clinical studies of abuse liability. Products that increase blood pressure or heart rate will require more extensive blood pressure assessments, such as ambulatory blood pressure monitoring in a subset of patients.

Statistical Issues
Historically, there have been high rates of premature subject withdrawal in long-term trials of obesity drugs. To allow for a true intent-to-treat (ITT) analysis, companies are encouraged to obtain body weight measurements in all subjects who prematurely withdraw from clinical trials near the calendar date at which they were scheduled to complete the trial. A sensitivity analysis should be conducted that considers subjects who are treated, drop out, and do not have complete post-baseline data as treatment failures. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results. If statistical significance is achieved on the co-primary endpoints, type 1 error should be controlled across all clinically relevant secondary efficacy endpoints intended for product labeling.

V. Cardiovascular Trials in Patients with Obesity

As discussed below, only two controlled trials have been conducted to examine the effects of drug-induced weight loss on CV events.

Sibutramine and SCOUT

Sibutramine was approved by for the treatment of obesity in 1997. Sibutramine was recommended for obese patients with an initial BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with other risk factors (e.g., diabetes, high cholesterol, controlled high blood pressure). Sibutramine produces its therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition.

Treatment with sibutramine was associated with mean increases in systolic and diastolic blood pressure of 1 to 3 mm Hg and with mean increases in pulse rate of 4 to 5 beats per minute relative to placebo. These effects were similar in normotensives and in patients with hypertension controlled with medication.

In November 2009, FDA issued an early communication about an ongoing safety review of sibutramine based on preliminary data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT).[21] SCOUT was initiated in 2002 and enrolled ~10,000 overweight or obese patients with diabetes and/or a history of coronary or peripheral vascular disease or stroke, along with other CV risk factors.[22] Patients randomized to sibutramine had an increased risk of MACE – nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, or resuscitated cardiac arrest – compared with patients randomized to placebo[23].

In January 2010, the FDA required contraindications on the sibutramine label, cautioning that the drug should not be used in patients with a history of coronary artery disease (e.g., heart attack, angina), stroke or transient ischemic attack, heart arrhythmias, congestive heart failure, peripheral arterial disease, or uncontrolled hypertension (e.g., > 145/90 mmHg).

Later in January 2010, the European Medicine's Agency's Committee for Medicinal Products for Human Use recommended the suspension of sibutramine and the drug was withdrawn from the European market.[24]

In September 2010, published data from SCOUT showed that over a mean 3.4 years of treatment, the incidence of MACE was 11.4% of patients randomized to sibutramine compared to 10% of patients randomized to placebo [HR 1.16 (95% CI 1.03, 1.31), p=0.015].[25]

In the on-drug population, 7.9% (385) of subjects randomized to placebo versus 9.5% (465) of subjects randomized to sibutramine had a MACE [HR 1.21 (1.05, 1.43), p<0.01]. The hazard ratios for nonfatal myocardial infarction and nonfatal stroke were 1.28 (1.04, 1.57) and 1.36 (1.04, 1.77), respectively. The hazard ratios for CV death and resuscitated cardiac arrest were 0.99 (0.82, 1.19) and 1.58 (0.61, 4.08), respectively.

21 Food and Drug Administration. Early communication about an ongoing safety review of Meridia (sibutramine hydrochloride). November 20, 2009.
22 Torp-Pedersen C, Caterson I, Coutinho W, et al. Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial. *Eur Heart J* 2007; 28:2915-2923.
23 European Medicines Agency. Press release 21 January 2010. www.ema.europa.eu/pdfs/human/referral/sibutramine/3940810en.pdf.
24 European Medicines Agency. Questions and answers on the suspension of medicines containing sibutramine. 21 Jan 2010 http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sibutramine_107/WC500094238.pdf (accessed Aug, 26, 2010).
25 SCOUT Investigators. Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects. N Engl J Med 2010; 363:905-17.

An advisory committee meeting was held in September 2010 to discuss the results of SCOUT. Eight of 16 committee members recommended that sibutramine be withdrawn from the market because its CV risks outweighed the drug's benefits. Most committee members believed that the available data did not support blood pressure or pulse monitoring as a clear way to mitigate the risk of a CV event associated with use of sibutramine. Many committee members said that even though sibutramine reduces body weight, there should be evidence of other accompanying benefit, such as CV benefit or improved glucose parameters.

In October 2010, FDA asked Abbott Laboratories to remove sibutramine from the market because it had an unfavorable benefit-risk profile. Abbott complied with FDA's request.

Rimonabant and CRESCENDO
Rimonabant was an oral antagonist/inverse agonist of the cannabinoid 1 (CB1) receptor. Its purported mechanisms of action are via a centrally-mediated regulation of appetite, as well as a gastrointestinal-tract-mediated modulation of satiety.

With treatment up to one year, rimonabant 20 mg once-daily reduced body weight by approximately 5% relative to placebo in overweight and obese non-diabetic subjects. As with other obesity drugs, the weight-loss efficacy of rimonabant was attenuated in overweight or obese subjects with type 2 diabetes.[26]

Rimonabant-associated weight loss was accompanied by improvements in levels of triglycerides, HDL-C, and HbA1c. Relative to placebo, rimonabant had no effect on levels of total cholesterol or LDL-C, and reductions in systolic and diastolic blood pressure were less than expected given the degree of weight loss.

The following safety concerns were highlighted at the 2007 FDA advisory committee meeting for rimonabant:

- An approximate doubling in the risk of psychiatric adverse events, specifically depression, anxiety, insomnia, and mood disturbances
- An approximate doubling in the risk of suicidality, specifically suicidal ideation
- An increase in a constellation of neurological adverse events of unclear significance
- A possible increase in seizure risk

This advisory committee panel voted unanimously that the benefits of rimonabant did not outweigh its risks. The drug was not approved in the U.S.

Rimonabant, however, received marketing approval from the European Medical Agency (EMEA) in June 2006. On October 23, 2008, the EMEA issued a press release stating its Committee for Medical Products for Human Use had concluded the benefits of rimonabant no longer outweighed its risks, and subsequently recommended the product

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26 Egan, AG. FDA Clinical Review of NDA 21888 ZIMULTI[TM] (rimonabant)

be suspended from the UK market. Approval of the drug was officially withdrawn by the EMEA on January 16, 2009. This action was taken following an assessment of data indicating that many patients were taking rimonabant for short periods of time, and thus were not realizing the potential benefits of long-term weight reduction, yet they were assuming risk of serious psychiatric adverse events including suicide.

Meanwhile, the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial had been initiated in 2005 to test whether long-term rimonabant therapy would reduce the risk of MACE (CV death, nonfatal myocardial infarction, or nonfatal stroke) in a population with either documented CV disease or significant risk factors for development of atherosclerotic vascular disorders.[27]

Approximately 19,000 patients who had, or were at increased risk of, vascular disease were randomly assigned to receive either rimonabant 20 mg (n=9381) or matching placebo (n=9314). At a mean follow-up of 13.8 months, the trial was prematurely discontinued because, as aforementioned, health regulatory authorities determined that the drug's benefit-risk profile was no longer positive.

At the close of the trial in November 2008, MACE occurred in 364 (3.9%) patients assigned to rimonabant and 375 (4.0%) assigned to placebo (hazard ratio 0.97, 95% CI 0.84–1.12, p=0.68).

With rimonabant vs. placebo, gastrointestinal (3038 [33%] vs 2084 [22%]), neuropsychiatric (3028 [32%] vs 1989 [21%]), and serious psychiatric side effects (232 [2.5%] vs 120 [1.3%]) were significantly increased. Four patients in the rimonabant group and one in the placebo group committed suicide during CRESCENDO.

Key features of the SCOUT and CRESCENDO trials are provided in Table 4.

Table 4. Summary of SCOUT and CRESCENDO Trial Design and Results

	SCOUT (sibutramine)	CRESCENDO (rimonabant)
Timeline	Conducted from 1/2003 to 3/2009	Enrollment 12/2005 to 7/2008. Trial ended 11/08
Primary endpoint	MACE defined as CV death, nonfatal MI, nonfatal stroke, and resuscitated cardiac arrest	MACE defined as CV death, MI, and stroke
Secondary endpoint	•Death due to any cause •First nonfatal or fatal MI •First nonfatal or fatal stroke •CV death •First MACE and/or revascularization procedure	First occurrence of •Any MI, •Any stroke, •CV death, or •Hospitalization for CV cause (UA, TIA, cardiac rhythm disorder,

27 Topol EJ, Bousser MG, Fox KA, Creager MA, Despres JP, Easton JD, Hamm CW for The CRESCENDO Investigators. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet 2010; 376: 517–23

	SCOUT (sibutramine)	CRESCENDO (rimonabant)
	•First hemodialysis or renal transplant	CHF, syncope, or urgent revascularization procedure)
General trial design	**Superiority trial** R, DB, PC with 6-wk lead in period on sibutramine, trial of sibutramine vs placebo	**Superiority trial** R, DB, PC trial of rimonabant vs placebo
Statistical Analysis Plan	Estimated enrollment of 9000 subjects (4500 in each group) and to continue the study until 2160 confirmed primary outcome events had occurred to have 80% power to detect an 11.4% reduction in the hazard ratio with sibutramine as compared with placebo, assuming a 7% annual event rate with placebo and a 30% rate of discontinuation of sibutramine, at a two-sided type I error rate of 0.05.	A yearly event rate of 3% for the composite MACE was assumed, requiring study of 8500 patients per group, with a total of 1600 events, to detect an overall 15% risk reduction with 90% power, two-sided type I error rate of 0.05, log-rank time from randomization to the occurrence of an event of the composite.
Major Inclusion Criteria	•Men and women, age 55 years and older •BMI ≥ 27 kg/m^2 and < 45 kg/m^2 or •BMI > 25 kg/m^2 and < 27 kg/m^2 with increased waist circumference •At risk for CV events: –History of CV disease, cerebrovascular disease, PVD OR –History of T2DM with ≥ 1 other CV risk factor (HTN, dyslipidemia, current smoking, or DM neuropathy)	•Men and women aged 55 or greater, **AND** •Abdominal obesity, with a waist circumference > 102 cm (40 inches) for males and > 88 cm (35 inches) for females on 3 successive measurements at baseline visit, **AND** • either coronary, cerebrovascular, or peripheral artery disease in the past 3 years, or at least two major CV risk factors[28]
Major Exclusion criteria	Symptoms of heart failure > NYHA functional class II, BP > than 160/100 mm Hg, HR > 100 bpm, scheduled cardiac surgery or coronary angioplasty, or a weight loss of more than 3 kg within the previous 3 months	Obesity due to known endocrine disorder, pregnancy or plans to become pregnant, breastfeeding, very low-calorie diet (1200 calories or less a day) or bariatric surgery within prior 6 months, other condition (medical, psychological, social, or geographical) or a CV condition likely to require an invasive intervention within 1 month after randomization
Demographics of Patient Population	58% men; 96% white; mean age 63 years; weight 96 kg; BMI 34 (M), 35 (F); DM only ~25%; CV only ~16%;	64% men; 84% white; mean age 64 years; BMI 33; DM 60%; HTN 88%; MI 36%; stroke 17%

28 Documented coronary heart disease was defined as hx of MI, multivessel CAD by angiography, previous coronary intervention, or bypass grafting. Cerebrovascular disease was defined as ischemic stroke or TIA with abnormal MRI or CT. Peripheral artery disease was documented by a hx of intermittent claudication and either an abnormal ankle-brachial index or vascular procedure. Risk factors included T2 DM, abdominal obesity and at least two additional factors of the metabolic syndrome, renal artery disease, advanced age (men >65 years, women >70 years), asymptomatic cerebrovascular or peripheral artery disease, and raised high-sensitivity C-reactive protein.

	SCOUT (sibutramine)	CRESCENDO (rimonabant)
Randomized	CV-DM 59%	
Study duration	3.4 yrs	13.8 months (1.15 yrs)
Number of patients	10,744 (4906 sibutramine vs 4898 placebo)	18,696 (9381 rimonabant vs 9314 placebo)
Number of sites	298 centers in countries in Europe, Central America, South America, Australia	974 hospitals in 42 countries
MACE annualized event rate in control group	~2.9% (10%/3.4 yrs)	~3.5% (4%/1.15 yrs)
Primary efficacy analysis (ITT population)	11.4% (561/4906 events) in sibutramine group vs 10.0% (490/4898) in placebo [HR 1.16 (1.03, 1.31), p=0.015]	3.9% (364/9381 events) in rimonabant group vs 4.0% (375/9314 events) in placebo [HR 0.97 (0.84, 1.12), p=0.68]

VI. Cardiovascular Assessment of Drugs for the Treatment of Type 2 Diabetes Mellitus (T2DM)

Despite evidence of clinical benefit from HbA1c reduction in both Types 1 and 2 diabetes mellitus, questions have been raised as to whether long-term CV trials should be part of the approval process for anti-diabetic medications in T2DM given recent controversies surrounding the CV safety of Avandia (rosiglitazone). Therefore, FDA convened a 2-day advisory committee meeting in July 2008 to discuss the role of CV assessment in the pre-approval and post-approval settings for drugs developed for the treatment of type 2 diabetes mellitus.[29] After considering the recommendations of the advisory panel and other data, FDA published a guidance for industry in December 2008 entitled, *Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.*[30]

This guidance states that pharmaceutical companies developing new drugs for the treatment of type 2 diabetes should show that these therapies do not result in an unacceptable increase in CV risk. The guidance calls for evaluation of whether the treatment increases CV risk; it does not ask pharmaceutical companies to show a CV benefit with their product. It was believed that a requirement to show CV benefit would have substantially delayed availability of new treatments for type 2 diabetes, as it has not

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29 Role of cardiovascular assessment in the preapproval and postapproval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus. In: Dockets for July 1–2, 2008, endocrinologic and metabolic drugs advisory committee meeting. United States Food and Drug Administration. 2008. http://www.fda.gov/ohrms/ dockets/ac/cder08.html#EndocrinologicMetabolic. Accessed 13 Jan 2012.
30 Guidance for industry: Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. In: Guidances (drugs). United States Food and Drug Administration. 2008. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/ucm071627.pdf. Accessed 13 Jan 2012.

been possible, even in large outcome trials, to conclusively show such benefit in type 2 diabetes for any therapies, including insulin.

In order to identify off-target CV toxicity, the evaluation of CV risk applies even if there is no known CV signal with the investigational agent in animals or humans, or a history of concern with the pharmacologic class.

To generate reliable data on CV risk, the guidance recommends that pharmaceutical companies establish an independent CV endpoint committee to prospectively and blindly adjudicate MACE during phase 2 and 3 clinical trials. The guidance also recommends that the phase 2 and 3 clinical trials be designed so that a pre-specified meta-analysis of MACE can be reliably performed. In addition, the guidance recommends that the phase 3 program enroll patients at increased CV risk and that the trials be of sufficient duration to ensure an adequate number of CV events and obtain long-term safety data.[31]

The guidance recommends that pharmaceutical companies compare the incidence of MACE with the investigational drug to the incidence of these events with comparators. Based on this comparison, the company calculates the point estimate for the risk ratio or hazard ratio and its corresponding two-sided 95% confidence interval. The upper bound of the 95% confidence interval represents a reasonable estimate of the worst case for increased CV risk. The rationale that supports these upper boundary thresholds is based in part on sample sizes (for example, an upper bound of 1.2 would require exceptionally large sample sizes) and in part on an unacceptable level of risk demonstrated with other therapies for the treatment of diabetes. For the CV data to support approvability of a new diabetes drug, this upper bound should be less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval, a postmarketing CV trial generally will be required to show definitively that this upper bound is less than 1.3. If the premarketing data were to show that this upper bound is less than 1.3, and the overall risk-benefit analysis supports approval, a postmarketing CV trial generally may not be necessary. Reassuring evidence that an anti-diabetic therapy does not confer CV risk exceeding 1.3 will generally require a dedicated CV outcomes trial in high CV-risk patients.

VII. Cardiovascular Assessment of Drugs for the Treatment of Obesity

Trial Design Issues

The next section will briefly discuss some of the trial design challenges and considerations for CV outcomes trials (CVOT) for drugs indicated to treat obesity.

1. Superiority vs Non-Inferiority CVOT

The primary objective of the CVOT is to show CV benefit (superiority to placebo) or to rule out an unacceptable increase in CV risk (non-inferiority to placebo). In general,

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31 Joffe HV, Parks MH, Temple R. Impact of cardiovascular outcomes on the development and approval of medications for the treatment of diabetes mellitus. Rev Endocr Metab Disord. 2010;11:21-30

demonstration of superiority will require a larger sample size than demonstration of non-inferiority, assuming the same true relative risk (less than 1.0) for both analyses.

If the objective is non-inferiority, the degree of unacceptable CV risk that should be ruled out will need to be considered. A related issue is whether the noninferiority margin should be the same for all obesity drugs or vary in relation to the specific perceived risks and benefits of individual drugs.

Table 5 provides required sample sizes, in terms of both number of primary CV events and patient-years needed to observe these events, as functions of different annual event rates and non-inferiority margins measured as relative risks. The table assumes 90% power and a true hazard ratio of 1 with testing carried out at the two-sided $\alpha=0.05$ level.

Note that Table 5 also provides the excess CV risk, as measured by the risk difference (RD) that can be ruled out. If the annual event rate turns out to be *higher* than the assumed rate, the selected relative risk margin *will not* preserve the RD to exclude. If the rate turns out to be **lower** than expected, the selected relative risk margin *will* rule out a smaller RD.

Table 5: Sample Size Calculations

Event Rate (per 100 subject years)		Relative Risk								
		1.3	**1.4**	**1.6**	**1.8**	**2.0**	**2.5**	**3.0**	**3.5**	**4.0**
0.5	RD	0.15%	0.20%	0.30%	0.40%	0.50%	0.75%	1.00%	1.25%	1.50%
	EE	1.5	2.0	3.0	4.0	5.0	5.0	10.0	12.5	15.0
	Events	610	371	190	121	87	50	34	26	21
	PY	122000	74200	38000	24200	17400	10000	6800	5200	4200
	PE	1.11	1.14	1.20	1.26	1.32	1.44	1.54	1.64	1.73
1.0	RD	0.30%	0.40%	0.60%	0.80%	1.00%	1.50%	2.00%	2.50%	3.00%
	EE	3.0	4.0	6.0	8.0	10.0	15.0	20.0	25.0	30.0
	Events	610	371	190	121	87	50	34	26	21
	PY	61000	37100	19000	12100	8700	5000	3400	2600	2100
	PE	1.11	1.14	1.20	1.26	1.32	1.44	1.54	1.64	1.73
1.5	RD	0.45%	0.60%	0.90%	1.20%	1.50%	2.25%	3.00%	3.75%	4.50%
	EE	4.5	6.0	9.0	12.0	15.0	22.5	33.0	37.5	45.0
	Events	610	371	190	121	87	50	34	26	21
	PY	40667	24734	12667	8067	5800	3334	2267	1734	1400
	PE	1.11	1.14	1.20	1.26	1.32	1.44	1.54	1.64	1.73

RD = Risk Difference (Rate Active minus Rate Control)
EE = Excess Events (Events Active minus Events Control)
Events = Number of events required for 90% power
PY = Patient years need to observe required events
PE = Maximum value of point estimate for RR in order to meet upper bound threshold.

2. Primary Cardiovascular Endpoint for a CVOT

Trials designed to show CV benefit often, but not always, use a primary composite endpoint of MACE that includes CV death, non-fatal myocardial infarction and non-fatal stroke (strict MACE). Trials sometimes include other endpoints in the primary composite, such as hospitalization for unstable angina and/or arterial or coronary revascularizations (MACE-Plus). A concern with the use of MACE-Plus is the "softer" endpoints such as revascularizations or hospitalization for unstable angina are more subjective, can be challenging to define, and their occurrence may differ depending on the local standards of care. The variability of these more subjective endpoints can bias the trial results towards the null, which is of particular concern for non-inferiority trials.

3. Baseline Characteristics of the Patient Population for a CVOT

For an event-driven CVOT, an annual MACE rate of 0.5% in the control group would require large numbers of subjects and/or longer durations of treatment in order to observe the required number of events. Enrichment of a CVOT with overweight and obese subjects with higher annual MACE rates would ensure more events while subjects are on drug. However, it has been argued that a sizable portion of individuals prescribed obesity drugs do not have high annual MACE rates (e.g., women in their mid-40s). Thus, while enrichment of CVOT for obesity drugs with patients at high risk for CV events may reduce or limit generalizability of the trial results, this approach allows one to demonstrate acceptable CV safety in a high-risk population which then can be generalized to a lower-risk population.

4. Timing of Interim Analyses of a CVOT

While an interim analysis of MACE may be statistically valid in a CVOT of an obesity drug, there are clinical concerns regarding the mean duration of drug exposure prior to the analysis. The weight-loss efficacy for many obesity drugs is usually greatest at 6-9 months after initiation of therapy and often wanes thereafter. If the weight-loss efficacy of an obesity drug diminishes over time, its CV efficacy/safety profile may change over time as well. Thus, the timing of an interim analysis, the results of which may provide the basis for regulatory approval of an obesity drug, needs to be determined carefully.

5. Primary Analysis Population for a CVOT

Given the historically high drop-out rates in trials of obesity drugs, it is important to identify the appropriate patient population for the primary analysis of a CVOT. While an intention-to-treat (ITT), or an on-treatment and off-treatment, population takes into account data from subjects who have dropped out of the trial and is generally considered the most appropriate population for primary efficacy analyses, an on-treatment population may provide more information regarding the "true" CV efficacy/safety of an obesity drug.

VIII. Conclusions

Obesity affects millions of people in the United States and increases the risk of premature death and CV disease. Thus, the CV assessment of drugs developed for the treatment of obesity is an important public health issue. We look forward to a thorough discussion of this complex matter on March 28 and 29. Please keep in mind the following discussion points and voting question as you prepare for the meeting.

IX. Draft Points for Discussion

1. The current draft obesity drug guidance document recommends that at least 3000 patients be randomized to investigational drug therapy and at least 1500 to placebo in one-year phase 3 trials. To date, most of the patients enrolled in the phase 2 and 3 clinical trials for investigational obesity drugs have very low short-term risk for major adverse cardiovascular events (MACE) (e.g., < 0.5% per year).

   Discuss the potential strengths and weaknesses of enriching the phase 2 and 3 clinical trials with overweight and obese individuals at higher risk for CV events (e.g., history of myocardial infarction, stroke, multiple risk factors) and performing a meta-analysis of prospectively adjudicating MACE.

2. For drugs with a signal for potential CV harm, it should be assumed that sponsors will be required to rule out a certain degree of excess CV risk; e.g., through conduct of a dedicated CV outcomes trial (CVOT) prior to market approval.

   Discuss the potential strengths and weaknesses of the following design parameters of a CVOT for an obesity drug:

   a. Ruling out a certain degree of excess CV risk with a pre-approval analysis of a fraction of the planned number of total events, followed by ruling out a smaller excess CV risk with the post-approval final analysis. This assumes that the pre-approval analysis will be based largely on data obtained during the first year of patient exposure, a period of fewer drop outs and maximal weight loss.
   b. Setting non-inferiority margins for excess CV risk on the basis of risk difference versus relative risk.
   c. Primary endpoint of strict MACE (CV death, nonfatal MI, nonfatal stroke) versus MACE-Plus (e.g., hospitalized unstable angina, emergent coronary revascularization).
   d. Primary analysis population that incorporates on-treatment and off-treatment information (total time analysis population) versus a population that incorporates only on-drug information (on-drug analysis population).

    e. Discontinuing from study drug patients who do not achieve a certain degree of weight loss within the first 3 to 6 months of the trial. Those withdrawn from study drug would continue to be followed.

3. Do you believe that obesity drugs <u>without</u> a signal for CV harm should be required to rule out a certain degree of excess CV risk with a CVOT or an appropriately sized meta-analysis of phase 2 and 3 MACE data?

    a. If yes, please discuss how (CVOT or meta-analysis or both) and when such data should be obtained:

        I. Pre-approval
       II. Pre- and post-approval (two-staged approach with different non-inferiority margins pre- and post-approval)
      III. Post-approval

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