FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

THURSDAY, JULY 15, 2010

8:00 a.m. to 4:30 p.m.

Hilton Washington, D.C. North/Gaithersburg

620 Perry Parkway

Gaithersburg, MD

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P R O C E E D I N G S

(8:00 a.m.)

DR. BURMAN: I'd like to remind everyone present to please silence your cell phones, BlackBerrys, and other devices if you have not already done so. I would also like to identify the FDA press contact, Ms. Karen Riley, who's to my left.

Thank you, Ms. Riley.

My name is Ken Burman. I'm chair of the Endocrinologic and Metabolic Drugs Advisory Committee. I will now call the meeting of the Endocrinologic and Metabolic Drugs Advisory Committee to order.

We would like to go around the room and please introduce yourself. We will start with the FDA and Dr. Curtis Rosebraugh to my left.

DR. ROSEBRAUGH: Curt Rosebraugh, director, Office of Drug Evaluation II.

DR. COLMAN: Eric Colman, deputy for DMEP, FDA.

DR. ROBERTS: Mary Roberts, clinical reviewer for DMEP, FDA.

DR. ROGAWSKI: Michael Rogawski, professor

of neurology at the University of California, Davis.

DR. MORRATO: Elaine Morrato, in the Department of Health Systems Management and Policy, University of Colorado, Denver.

DR. HENDERSON: Jessica Henderson. I'm the consumer representative. I'm here from Oregon.

DR. GOLDFINE: Allison Goldfine, associate professor, Harvard Medical School and head of Clinical Research, Joslin Diabetes Center.

DR. PROSCHAN: Michael Proschan. I'm a mathematical statistician at NIAID.

DR. BURMAN: Ken Burman. I'm chief of endocrinology at the Washington Hospital Center and professor of medicine at Georgetown University.

DR. TRAN: Paul Tran, the DFO for the Endocrinologic and Metabolic Drug Advisory Committee.

DR. FLEGAL: Katherine Flegal, epidemiologist from the National Center for Health Statistics, Centers for Disease Control and Prevention.

DR. THOMAS: Abraham Thomas, division head, Endocrinology, Henry Ford Hospital, Detroit.

DR. BERSOT: Tom Bersot, professor of medicine in the Division of Endocrinology at the University of California San Francisco.

DR. WEIDE: Lamont Weide, chief of Endocrinology at University of Missouri, Kansas City School of Medicine, Truman Medical Centers, professor of medicine.

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DR. HENDRICKS: Ed Hendricks, private practice, Sacramento, California.

MS. COFFIN: Melanie Coffin, patient representative.

DR. CRAGAN: Janet Cragan from the National Center on Birth Defects and Developmental Disabilities at Centers for Disease Control and Prevention.

DR. HECKBERT: Susan Heckbert, professor of epidemiology, University of Washington.

DR. VELTRI: Rick Veltri, industry representative.

DR. CAPUZZI: David Capuzzi, Thomas Jefferson University.

DR. BURMAN: Thank you. I would also like to announce that Dr. Jules Hirsch is unable to come today, and that's the reason there is an opening.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the

committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

DR. TRAN: The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drug Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with the federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in

compliance with the federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for the purpose of 18 USC Section 208, their employers.

These interests may include investments,

consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of the safety and efficacy of New Drug Application NDA 22-580, proposed trade name Qnexa, phentermine and topiramate, controlled release capsules by Vivus, Incorporated, as an adjunct to diet and exercise for weight management in patients with a body mass index greater than equal to or 30 kilograms per meter square, or a body mass index equal or greater than 27 kilograms per square meter if accompanied by weight-related comorbidities.

This is a particular matters meeting, during which specific matters related to Vivus product Qnexa will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they

have made concerning the product at issue.

With respect to the FDA-invited industry representative, we would like to disclose that Dr. Enrico Veltri is participating in today's meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Veltri's role at this meeting is to represent industry in general and not any particular company. Dr. Enrico Veltri is employed as an independent pharmaceutical consultant. Dr. Veltri is a former employee of Merck and currently holds Merck stocks.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participant needs to exclude himself from such involvement, and that exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BURMAN: We will now proceed with the FDA opening remarks from Dr. Eric Colman. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

DR. COLMAN: Good morning. I'd first like to thank the new panel members who are just joining us for today's meeting. And I'd like to thank the members who have endured the past two days and didn't resign last night and go home. But we will be covering your therapy for PTSD.

[Laughter.]

DR. COLMAN: So I think, as everyone knows, we're here to discuss the safety and efficacy of a combination drug product that includes topiramate, which is a compound that was approved in 1996 for the treatment of seizures, and phentermine, which is a drug that's been around a long time, since the late 1950s, and is currently labeled as a therapy for weight loss but just for a few weeks duration, so short-term duration in the labeling.

In general, the FDA is in agreement with the company with respect to the weight loss effects of the drug that's been proposed, trade name of Qnexa. So you will see during the FDA presentation that the focus is primarily on safety.

We have five general categories of safety: psychiatric-related adverse events, cognitive-related adverse events, metabolic acidosis, cardiovascular safety summary, and perhaps most importantly, we want to deal and discuss whether topiramate poses a risk for teratogenicity when used in this combination product.

You should be happy to know there's only one FDA presentation today. And I have never heard Mary argue with herself, so I think it should be a fair amount of harmony. So I think, with that, we can get the show on the road.

DR. BURMAN: Thank you very much.

We will now proceed with the sponsor presentations. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not

participate, except at the specific request of the panel.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationship that you may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

Welcome.

DR. GESUNDHEIT: Good morning. My name is Neal Gesundheit. I am an endocrinologist and associate professor of medicine at Stanford University, and a clinical advisor to Vivus, Incorporated. My background is that I completed medical residency at Stanford and fellowship in endocrinology and metabolism at the National Institutes of Health.

From 1994 to 1999, I was the vice president of Clinical and Regulatory Affairs at Vivus, and have remained an advisor to the company. In 1999, I joined the Stanford faculty in the Department of Medicine. Any opinions expressed today are my own and not those of Stanford University. I am a shareholder and a paid advisor to Vivus.

My co-moderator is Dr. Wesley Day. Dr. Day completed his doctorate in pharmacology and toxicology at the University of Maryland, Baltimore. He has been the vice president of Clinical Development at Vivus since 2005, and has been the architect of the Qnexa clinical trial program. Dr. Day is an adjunct

associate professor at the University of Maryland, Baltimore School of Pharmacy.

We are grateful for this opportunity to present to the advisory committee, the division, and the public.

Qnexa contains low doses of two approved drugs. Phentermine was approved in 1959 for short-term treatment of obesity. It is the most widely prescribed obesity treatment in the U.S., with over six million prescriptions in 2009. Its mechanism is that elicits the central release of norepinephrine, which has an appetite-suppressing effect.

The other component is topiramate, which was approved in 1996 as a treatment for epilepsy and in 2004 for migraine prophylaxis. There were over nine million prescriptions written for topiramate in 2009. Its mechanism, useful for the management of obesity, is that it can increase satiety, it alters taste, and it may have other metabolic effects.

Qnexa is a novel combination containing lower doses of these two previously approved agents. As shown in this diagram, phentermine is approved at a

top dose of 30 milligrams daily, and topiramate at a top dose of 400 milligrams per day. The combinations in Qnexa contain one-half, one-fourth, and one-eighth of the top approved dose of phentermine, and approximately one-fourth, one-eighth, and one-sixteenth of the top approved dose of topiramate.

The combinations are shown by the blue lines. Note that mid and low doses of Qnexa contain proportionately half and then one-fourth of the top amount of the drug. The ratio of phentermine to topiramate is constant, at a ratio of approximately 1:6, milligram per milligram. In this presentation today, we will refer to doses as low, mid, and top, as shown in this diagram.

The proposed indication is that Qnexa is indicated for the treatment of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with diet and exercise. Qnexa is recommended for obese patients. That would be individuals with body mass indices greater than or equal to 30 kilograms per meter squared, or overweight patients with BMIs greater than or equal to 27 with

weight-related comorbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity.

Our agenda this morning is that our first presenter will be Dr. Louis Aronne, who is a clinical professor of medicine at Weill Cornell Medical College. He will speak about the current medical need. Then Dr. Day from Vivus will talk about the clinical program and the efficacy of Qnexa. I will then review the general safety, followed by Dr. Kishore Gadde, who is the director of the clinical trials program at Duke University Medical Center, who will speak about the neuropsychiatric safety aspects.

We will then be followed by Dr. Gideon Koren, who is the director of the Motherisk program at the Hospital for Sick Children at the University of Toronto. Dr. Koren has multiple academic appointments, both with the University of Toronto and the University of Western Ontario. He will speak about pregnancy issues. And then I will return to discuss the risk mitigation program and summarize the overall risks and benefits of Qnexa.

Please allow me to introduce our panel of

experts. Dr. David Allison is a statistician and an expert in obesity research. Dr. John DeSesso is a developmental and reproductive toxicologist, teratologist, and embryologist. Dr. Anthony Fossa is a cardiovascular pharmacologist. Dr. Hylar Friedman is a clinical pharmacologist. Dr. Sheryl Haut is a neurologist and an epilepsy expert.

Dr. Gary Kay is a neurophysiologist. Dr. Robert Mansbach is a behavioral pharmacologist. Dr. J.F. Marier is an expert in population PK/PD modeling. Dr. Craig Pratt is a cardiologist. Dr. Frederick Reno is a toxicologist. Mr. Michael Schwiers is our chief statistician. And Dr. Annette Stemhagen is an epidemiologist.

At this point I'd like to turn the program over to Dr. Aronne.

DR. ARONNE: Good morning. My name is Dr. Louis Aronne. I'm a clinical professor of medicine at Weill Cornell Medical College. I'm a consultant to Vivus. I've been an investigator in the trials, but I have no stock ownership interest in the company.

For 24 years, I've treated obesity at New York Presbyterian Weill Cornell Medical Center, where I am director of the Comprehensive Weight Control Program. I'm a past president of the Obesity Society, and I edited the National Institutes of Health Practical Guide to Obesity Treatment, which was published in the year 2000.

One of every three adults in the United States have an increased body weight that could put their health at risk. Obesity is associated with a significant increase in mortality from cardiovascular disease, cancer, diabetes, and kidney disease, and is associated with more than 50 illnesses.

This translates into reduced life expectancy. For example, the diseases associated with obesity reduce life expectancy between 1 and 6 years for someone with a body mass index between 30 and 40, and up to 13 years for someone with a body mass index greater than 45.

The pathology of obesity is becoming clear. An excess production of some adipose tissue hormones and suppression of others, combined with recruitment

of inflammatory cells, appears to produce the many illnesses we associate with obesity, and explains how problems as disparate as arthritis, diabetes, heart disease, and cancer can all be increased in the obese.

While the appearance of multiple hormonal products acting in concert makes obesity powerful at causing disease, it makes obesity and weight loss a valuable target for improving health.

In many cases the relationship between obesity and disease risk can be steep. Here we see the prevalence of diabetes from the NHANES 1999 to 2004. It is tripled in grade 1 obese individuals, quadrupled with grade 2, increased seven times in those with grade 3, compared to the prevalence in normal weight individuals. Data suggest that 70 percent of diabetes cases in the United States are caused by excess weight.

Add to diabetes the many other illnesses that increase in prevalence with increased body weight, and it is easy to see how obesity adds to health care costs, and how obesity treatments can improve health and save health care dollars.

As a result of the known benefits of weight loss, federal agencies and national health organizations have recommended losing weight as first-line management for treatment of many chronic diseases, with an initial goal of a 10 percent weight loss. This has been easier said than done. We haven't been able to reach these goals consistently because of a complex neuroendocrine resistant mechanism meant to prevent starvation.

However, weight loss now appears to be like a gift that keeps on giving. The diabetes prevention program has shown that weight loss through diet and lifestyle will reduce the risk of developing diabetes for 10 years, and evidence presented at this year's American Diabetes Association meeting shows that the risk reduction through diet and lifestyle is maintained even longer.

To quote Dr. Frank Hu, winner of the Kelly West award, "It was remarkable that in the Chinese Da Qing Diabetes Prevention Study, there was still a 40 percent reduction in diabetes risk in the intervention group at 20 years follow-up, 20 years

after the initial intervention with no further treatment."

Now, thanks to our surgical colleagues, we have the SOS, Swedish Obese Subjects, prospective trial in which 2,000 bariatric surgery patients were matched to 2,000 control patients and followed long term. The mean weight loss at 10 years was 17 percent and ranged from 14 to 25 percent, depending upon the procedure.

This study produced a 29 percent reduction in all-cause mortality, a 48 percent reduction in myocardial infarction, and a 39 percent reduction in mortality due to cancer, an unexpected result but now understandable given our new knowledge about adipocyte biology. So weight loss not only produces improvements in the associated illnesses, but we can finally say that if you lose weight, you'll live longer.

Surgery is the gold standard for efficacy, but it remains a limited solution in fighting the twin epidemics of obesity and diabetes. While bariatric surgery is now safer than any procedure, including

cholecystectomy, thanks to the Centers of Excellence concept, the incidence of complications, depending upon the procedure, is, at a minimum, 5 in 100, and mortality is 1 in 1,000.

So there exists a gap in obesity treatment, a gap which has led the patient and physician to do nothing, to ignore each other, in the face of an epidemic. To bridge this gap, we need more effective nonsurgical treatment options, including those which are covered by health insurance, in patients who are at risk from their obesity. Let's look at an example of the success of a medical treatment.

Hypertension used to be called the silent killer. It is no more. Blood pressure measurement and the nuances of medical management are ingrained in most every primary care provider. We now have 100 medications in nine categories, so if one doesn't work or causes side effects, another is available.

Our understanding of the pathology and pathophysiology of obesity support medical treatment as an adjunct to diet and lifestyle in the treatment of obesity. The morbidity and mortality of obesity is

a huge burden on our patients and on our society. The medical need is urgent. It's clear we need new medical therapies to manage the epidemic of obesity. Thank you.

DR. DAY: Thank you, Dr. Aronne, members of the panel, audience, and members of the FDA. I'll present an overview of the efficacy associated with the various studies we've performed in the Qnexa program.

The Qnexa program has included a diverse population, ranging from overweight to obese to morbidly obese from overweight with significant comorbidities. We've studied three populations in phase 2 under a proof of concept idea, obese without comorbidities, poorly controlled obese diabetics, and severe sleep apneics that are obese.

In the phase 3 program, we performed three studies, a six-month factorial study to demonstrate combination guidelines for Qnexa, and two pivotal one-year studies focusing on high medical need populations. In 302 we studied morbid obese subjects with a minimum BMI of greater than 35. In 303 we

studied overweight to obese with the presence of at least two comorbidities, including hypertension, hypertriglycerides, and central adiposity. We also included in this study a small population of diabetics.

I will now talk about the phase 2 program that included approximately 450 subjects for proof of concept for weight loss, diabetes, and obstructive sleep apnea.

As Dr. Gesundheit mentioned, Qnexa is the combination of two low doses of two approved products, phentermine and topiramate. Based on the literature, it was known and recognized that both topiramate and phentermine had good weight loss properties. The issues with phentermine had to do with the doses necessary to achieve significant weight loss.

It was hypothesized that by combining the two agents, lower doses could be used, and these lower doses of the respective agents could potentially mitigate the tolerability issues that were associated with each agent in a monotherapy setting.

OB-201 was performed under the oversight of

Dr. Kishore Gadde at Duke University. This included 200 subjects that were treated for a period of six months. At the end of six months of treatment, the Qnexa-treated subjects lost an average of 25 pounds. This compared very favorably to the monotherapies, which were 13 and 10 pounds respectively, and all three groups were significant compared to placebo.

We learned from this study several factors that encouraged us to move forward with clinical development. We learned that the low doses used in Qnexa were effective. We learned that these low doses were tolerable. The retention in that study for Qnexa arm was 92 percent. We also learned that the weight loss was associated with a positive signal on comorbidities such as lipids and blood pressure.

Therefore, we performed another study looking at poorly controlled diabetic subjects. These were subjects that had a baseline HbA1c of 8.7 percent. All subjects were treated for six months, and we compared the top dose of Qnexa, 15 milligrams phentermine and 100 milligrams of topiramate, to placebo.

The background in this study was active management with antidiabetic medication, and consequently, we saw significant signal or reduction in the primary endpoint for placebo of .6 percent. This was accomplished with increased use of antidiabetic meds.

Importantly, Qnexa-treated subjects had a significantly greater reduction of 1.2 percent in the primary endpoint of HbA1c. And this reduction was accomplished with a decrease in the dosage of antidiabetic medications and a reduction overall in the use of type 2 medications compared to placebo. Thus, the greater improvement we saw in the primary endpoint of HbA1c was accomplished in the presence of the lower use of antidiabetic meds.

In this study we also confirmed other important endpoints. The diabetic subjects treated with Qnexa lost approximately 9 percent of their body weight. We saw significant improvements in blood pressure, lipids, and triglycerides.

The most recent study we've performed in the proof of concept setting was the study of Qnexa

effects on obstructive sleep apnea in obese subjects. This is our most recent study; it was not included as part of our NDA filing.

Using an overnight polysomnography lab, subjects were randomized at baseline with the presence of severe sleep apnea as defined by 30 events per hour of sleep. At the end of six months' treatment, Qnexa-treated subjects saw a 69 percent reduction in their number of sleep apneic events, bringing these subjects into the mild range of obstructive sleep apnea.

Because of the active background and the active management within the study, placebo subjects also benefitted. Placebo subjects had an average weight loss of about 5 percent. They also saw improvements in their sleep apneic parameters, with a reduction to 27.

Thus, the treatment of Qnexa resulted in significantly greater reduction of sleep apneic events compared to placebo. These subjects also saw significantly greater improvements in weight, blood pressure, lipids.

The results of our phase 2 program

encouraged us to move into an overall development plan for phase 3, which included three studies. OB-301 was our factorial study, six months' treatment in a combination setting compared to monotherapy, and our two pivotal one-year studies that were both designed with the concept of high medical needs subjects in a relevant target population of obese individuals.

Thus, the phase 3 program included over 4,500 subjects. OB-301, as I mentioned, was the smallest study, that was conducted for six months with the objective of demonstrating combination guidelines.

OB-302, that we call EQUIP, studied the top dose of Qnexa as well as the low dose compared to placebo. These were subjects that had a high BMI, average of 42. OB-303, that we call CONQUER, included obese subjects with significant comorbidities as determined at baseline. These comorbidities included hypertension, diabetes, hypertriglyceridemia, or the presence of excess waste.

The background program included the use of the LEARN program, a lifestyle and modification program, that provided background benefit for all

subjects in the trial.

The baseline demographics of OB-302 and OB-303 are different in that each study had specific objectives that required different populations. OB-302, as I mentioned, was in morbid obese individuals with lower presence of comorbidities. OB-303 had significant presence of comorbidities. Thus, 69 percent of the subjects in this study had hypertension, 57 percent had dyslipidemia, and approximately 16 percent were diabetic.

An important similarity between both programs was the presence of history of psychiatric disease, which ranged from 26 to 30 percent; a history of depression, ranging from 20 to 22 percent, which included the use of medications, antidepressant medications, primarily SSRIs, in some individuals. There was also a background rate of suicidal ideation of 3 to 4 percent. Demographically, both studies were similar with respect to race, ethnicity. The majority of subjects were female.

Looking at an integrated analysis of both of these studies for a completion rate, we noticed that

all treatment arms of Qnexa were significantly greater -- actually, the mid and the top dose were significantly greater than placebo. But all three treatment arms did have greater retention overall compared to placebo.

In this study, as with many clinical trials in this time frame, there's significant emphasis to retain subjects irregardless of their status on active or placebo treatment. Therefore, significant efforts were employed to maintain subjects within the trial despite the fact they may have dropped of drug for other reasons. Therefore, we see higher overall retention in subjects on or off drug of 71 percent on the top dose compared to study completion on drug. Thus, subjects completing on drug ranged -- a greater percentage ranged from 4 to 9 percent on Qnexa-treated arms.

There were two co-primary endpoints in 303 and 302 that were identical. These co-primary endpoints were dictated by the guidelines for weight loss. Both primary endpoints for all three treatment arms of Qnexa were significant. Weight loss for the

low dose was 5.1 percent in the continuous variable of percent weight loss, and 45 percent of subjects lost at lest 5 percent of their body weight.

For the top dose Qnexa, percent weight loss was 10.4 to 11 percent, and 67 to 70 percent of subjects treated with the top dose lost at least 5 percent. The mid dose fell in between the low and the top dose of 8.4 percent and 62 percent on the categorical weight loss feature. Thus, all three doses were significant, and all three doses met requirements for weight loss guidelines.

Looking closer at two additional categories of weight loss, and these two categories being 10 percent and 15 percent weight loss, these are important categories because they're recognized by important committees that have associated with greater weight loss with a greater degree of comorbidity effect. The E.U. guidelines also emphasize the need for attainment of at least 10 percent weight loss.

In these two categories, subjects treated with the top dose of Qnexa lost at least 15 -- 30 percent of subjects treated with the top dose lost

at least 15 percent of their body weight, and 47 percent of top dose-treated subjects lost at least 10 percent.

Weight loss in the mid dose was significant as well, with 19 percent of subjects losing at least 15 percent, and 37 percent of subjects treated with the mid dose losing at least 10 percent of their body weight on an ITT-LOCF basis.

Another examination of weight loss over time is presented in these two figures. These two figures illustrate Completers data. We see a strong dose-related response for all three treatment arms. We see that weight loss occurred early in study and are fairly rapid up to four months, with the top dose having a continued weight loss out to the end of study at week 56.

Looking at the left-hand figure, OB-302, we see that subjects treated with the top dose lost approximately 14.2 percent of their body weight, which would equate to about 37 pounds for these subjects if they were compliant on drug for the 56-week period. We see that the mid dose lost over 10 percent, on

average, in compliant individuals, and the low dose lost approximately 6 percent.

Looking at another weight-related variable, waist circumference reduction, waist circumference is an important surrogate for assessment of visceral adiposity. We see significant and dose-related decreases in waist circumference, as presented in this forest plot of placebo subtracted/least-squares mean difference data.

Looking at another way to assess the weight loss in this trial, we assessed weight loss by baseline BMI category. Again, all three doses, irrespective of their baseline BMI, saw significant weight loss. We see dose-related weight loss to the greatest degree in subjects with a BMI of greater than 40. This suggests that the top dose of Qnexa affords additional and greater benefit in subjects with a greater baseline BMI.

I'll now speak a bit about the effect of Qnexa treatment as it relates to improvements in hypertension, hyperlipidemia, and diabetes.

Systolic blood pressure is an important

surrogate of cardiovascular risk, and it's important that any drug that's used for treatment of weight loss should have neutral to meaningful improvements in this endpoint. Weight loss is expected to have improvements or reductions in systolic blood pressure.

In all studies in the phase 3 program, in all three doses, we see significant improvements in systolic blood pressure compared to placebo. In this forest plot, the placebo subtracted/least-squares mean difference for systolic blood pressure reductions was significant for all three doses.

Looking closer at the blood pressure endpoint, in a subpopulation identified as hypertensive at baseline, we examined a subset of subjects from OB-303 with a baseline systolic blood pressure of 135. Looking at this subpopulation, we see significant and dose-related reductions in the figure on the left for subjects treated with Qnexa, a 9.1 millimeter mercury reduction for top-dose Qnexa compared to 6.9 for the mid dose and 4.9 for placebo.

Again, as with our other studies, there was active management of antihypertensive medications in

this trial, and consequently, the improvements associated with placebo are also supported by some increase in the use of antihypertensive meds.

Looking at Qnexa-treated subjects, we see from 6 to 10 percent of subjects had an overall reduction in their use of meds. Thus, the reductions we see in blood pressure associated with weight loss and Qnexa treatment are occurring with the reduction in the use of medications in a small fraction of the subjects treated.

Looking at lipid endpoints for treatment with Qnexa, we examined triglycerides and HDL in a population of 303 subjects identified at baseline with elevated triglycerides greater than 200 mgs per deciliter. We see significant effects in all studies on the top dose of Qnexa. We also see significant effects in 303 and a positive trend in 301, and the low dose also demonstrated a positive trend.

Looking in the same population at the HDL effects in these same subjects, we see improvements or increases in HDL with Qnexa treatment in the top dose as well as the mid dose, significant for both of our

pivotal one-year trials. And we see important trends of improvement in the mid dose 301 and a neutral effect in our low dose.

Looking closer at a subpopulation -- I misspoke on the previous slide. The previous slide was all subjects on an ITT-LOCF basis. This is our subpopulation with baseline triglycerides of 238, on average. Looking at this population, we see a 24 to 25 percent reduction in least-squares mean change in this population, compared to an 8.8 percent reduction on placebo.

Again, looking at the subpopulation with elevated triglycerides at baseline, we see a 9 and a half to 10 percent increase in HDL for the mid and the full dose compared to 2.8 on placebo.

Looking at glycemic effects within this program, the subpopulation of diabetics that were treated in OB-303, identified at baseline, these were fairly well-controlled individuals with a baseline HbA1c of 6.8 percent. These subjects that were treated with both the mid and the full dose of Qnexa saw a .4 percent reduction, which was significantly

greater as compared to placebo.

As with the results in our OB-202 poorly-controlled diabetic trial, we see that the effects on the placebo-treated subjects occurred with an increase in the use of meds. Twelve percent of subjects on placebo had an overall increase in the use of meds, compared to less than 1 percent or 1 and a half percent for the mid dose of Qnexa. Thus, the overall reductions and improvements in glycemic endpoints for Qnexa-treated subjects are coming with a neutral effect on antihypertensive meds.

Looking closer at an important population with respect to risk, we looked at all non-diabetic subjects in OB-303. These were subjects identified as being non-diabetic at baseline, but progressing to diabetes by the end of the study. At the end of the study, they were characterized as diabetic if they had a fasting glucose greater than 126 or a two-hour OGTT greater than 200.

Examining this population across the various treatment arms, we see a 46 percent reduction in top dose-treated Qnexa subjects compared to placebo, and a

37 percent reduction in mid dose-treated subjects compared to placebo. The effects on the top dose were significant, and the effects on the mid dose had a p-value of .051.

Another important assessment in our program has been quality of life. We used the IWQOL instrument in all studies performed to date. The IWQOL is an instrument designed to assess quality of life in obese subjects. We also used SF-36, a well-recognized quality of life health function tool that's validated and recognized.

Looking at this instrument, we find significant effects by both the mid and the top dose for physical function, physical role, bodily pain, general health and vitality. We see neutral effects on social function, emotional, and mental health. Thus, the improvements that we see with Qnexa-treated subjects appears to extend into quality of life, seeing quality of life improvements in these treated subjects compared to placebo.

So in summary, of the Qnexa effects on efficacy, presented here is the mid dose summary in a

forest plot as well as the top dose on the right. To emphasize, we see dose-related effects on weight as well as dose-related effects on waist in both the mid and the top dose. We also saw significant effects on weight with the low dose that's not shown.

The whole spectrum of efficacy endpoints were significant with treatments of top dose. We saw significant improvements in blood pressure endpoints, inflammatory coagulation markers that I haven't discussed today such as CRP and fibrinogen. We also saw significant improvements in lipid endpoints such as HDL cholesterol, and glycemic endpoints, ranging from HbA1c, which I presented, to other important endpoints such as fasting insulin and HOMA assessment of insulin resistance.

We see dose-related improvements in mid dose-treated subjects for the same endpoints as well, but in some cases not to the same degree that we see with top dose. Thus, Qnexa treatment and associated weight loss was associated with significant improvements on comorbidities and the whole spectrum of weight-related effects and complications, as Dr.

Aronne has pointed out in his talk.

I'll now turn the lectern over to Dr. Gesundheit to talk about the safety.

DR. GESUNDHEIT: Thank you, Dr. Day.

This portion of the presentation will be divided into several parts. I will review the common adverse events, reasons for study discontinuation, and serious adverse events, forward by cardiovascular adverse events and laboratory parameters. After my presentation, Dr. Gadde will discuss the neuropsychiatric adverse events, and Dr. Koren will discuss pregnancy considerations.

The safety experience of Qnexa parallels the safety experience for its component parts, phentermine and topiramate. Shown here are the most common side effects reported with these two marketed products. For phentermine, these include dry mouth, insomnia, headache, dizziness, fatigue, and palpitations. For topiramate, these include paresthesia, fatigue, nausea, taste perversion or change, also called dysgeusia, somnolence, changes in attention, language, and memory, and changes in depression, anxiety, and

mood.

Shown here are the most common observed adverse events occurring in at least 5 percent frequency by preferred terms in the clinical investigational program of Qnexa. The most common three events, as you can see at the top of this figure, are dry mouth, paresthesia, and constipation, occurring at the top dose in between 16 and 20 percent of subjects at top dose of Qnexa.

The other adverse events shown occur with greater frequency at the top dose of Qnexa compared to placebo, and are distributed in a way that is consistent with the known side effects of topiramate and phentermine. There were no surprises.

Shown here are study discontinuation and completion rates during the clinical investigational program. As you can see overall on the top line, the patients randomized to mid and top dose of Qnexa had rates of study completion ranging between 72 and 75 percent, compared to placebo, where the completion rate was about 60 percent.

There is also another category of patients

who completed study while on drug throughout, and those numbers are somewhat lower. Those are shown in the second line. But again, the completion rate on drug was higher in subjects on the mid and top dose of Qnexa compared to placebo.

When we look at discontinuation of study drug due to adverse events, you can see that there is roughly a doubling at the discontinuation rate at the top dose of Qnexa compared to placebo. That's shown on the third line, approximately 17 percent discontinuation on Qnexa compared to 8 percent on placebo.

When one examines preferred terms, which explain the reasons for study drug discontinuation, you can see that there is no single preferred term that accounts for more than 2 percent of the reasons for discontinuation at the Qnexa top dose, although for the terms listed, the discontinuation rate, term by term, was higher in the Qnexa top dose-treated subjects compared with patients treated with placebo.

Discontinuations for other reasons, however, were higher in the placebo-treated subjects shown at

the bottom, almost 37 percent compared to 19 percent for Qnexa top dose. This accounts for the greater completion rate that was observed overall in the patients randomized to Qnexa.

Importantly, we examined serious adverse events and deaths. Serious adverse events are those that are most medically noteworthy, and these would include death, disability, hospitalization, prolonged hospitalization, and life-threatening illness. As you can see from this slide, these serious adverse events reported with placebo totaled 3.3 percent of subjects, and those on Qnexa, the rightmost column, also totaled 3.3 percent of subjects. There was one death that occurred in a patient randomized to placebo, and there were no deaths that occurred in any subject randomized to Qnexa.

We also examined issues that had been highlighted appropriately as potential areas of concern by the division. One of these areas is the change in heart rate that occurs in patients randomized to Qnexa. Shown here are the key vital signs, blood pressure, and heart rate in patients at

end of study compared to study entry in patients in the phase 3 program. As you can see from the top line, there was a significant reduction in systolic blood pressure at the top dose of Qnexa, as was outlined by Dr. Day. Placebo subtracted, this was 3.1 millimeters mercury reduction on Qnexa.

For diastolic blood pressure, there was about a 1 millimeter reduction, placebo subtracted. These changes in blood pressure were associated with a mean 1.6 beat-per-minute increase in the heart rate in Qnexa top dose compared to placebo. That's shown in the right lower corner.

We explored the possible significance of the increased heart rate accompanied by a decrease in blood pressure by examining the rate-pressure product. The rate-pressure product is simply the product of systolic blood pressure and simultaneous heart rate. It provides an estimate of myocardial oxygen demand, and it is shown here divided by 1,000.

As you can see from this slide, all subjects in all groups showed a slight lowering of the rate-pressure product at week 56 -- that would be at study

exit -- compared to baseline. For the top Qnexa group, the increase in the heart rate, which was accompanied, as we mentioned, by a decrease in blood pressure, translated to no change in the rate-pressure product compared to placebo, for a counterbalancing effect on this endpoint.

We also examined the effect of increased heart rate in rate-pressure product in subjects who were heart rate outliers. What this slide shows in the top part are patients who at any time during study had an increase of 10 beats per minute in their heart rate compared to baseline, and then on the bottom, those who had an increase or -- I'm sorry, those that had an increase of 20 beats per minute in the two lines that follow each other.

As you can see, if you look at the rightmost column compared to the leftmost column, more patients randomized to the top dose with Qnexa indeed had an increase by 10 and 20 beats per minute in their heart rate compared to those on placebo.

If one looks in the bottom part of the panel at a heart rate increase that was present on two or

more consecutive occasions or at study exit, one sees that the number of subjects showing these changes are lower than they are in the top panel. But nevertheless, there's an increase in the number of subjects with an increased heart rate in the Qnexa-treated groups.

In order to explore this further, looking at the patients who had an increase in heart rate, we look then at the blood pressure changes in these patients who showed the increase in heart rate. This slide shows on the left panel patients on placebo and the right panel those on Qnexa, and shows the change in systolic blood pressure at the time of the heart rate increase. The groups by change in heart rate are shown on the X axis, and the simultaneously-measured systolic blood pressure is shown on the Y axis.

As can be seen from the left panel, in patients who demonstrated increased heart rates on placebo, there was essentially no change in their systolic blood pressure. In contrast, in the right panel, patients randomized to the top dose of Qnexa showed a modest lowering of systolic blood pressure.

Thus, there was a lowering of systolic blood pressure on Qnexa at the same time that the heart rate was increased, similar to that which was observed in the population overall.

To determine the significance of the increase in heart rate and the simultaneous decrease in blood pressure, we looked further at the rate-pressure product in subjects who had a persistent heart rate of greater than 100. These would then be the heart rate outliers who on two or more occasions, or at study exit, had a heart rate greater than 100, and these would be potentially the subjects of greatest concern.

As one can see from the rightmost compared to the leftmost column, there were more subjects who met this definition, 17, in the top dose of Qnexa compared with placebo, where there were 10 subjects who met this definition. However, those subjects had a low -- those subjects on Qnexa had a lower systolic blood pressure, as you can see on the right column, and at the same time a lower diastolic blood pressure compared to the placebo subjects.

When one calculates the rate-pressure product in these heart rate outliers, the most extreme heart rate outliers in the entire program, one sees that the rate-pressure product was 12.8 in the patients on the top dose of Qnexa, shown in the rightmost column, while the rate-pressure product was 14.3 in the outliers under placebo treatment.

This suggests that in the heart rate outlier group on Qnexa, the rate-pressure product, if anything, is slightly lower and certainly no different than in the outliers randomized to placebo. Thus, in every analysis we performed, we see that the increase in heart rate is accompanied by a decrease in blood pressure and a neutral effect on the rate-pressure product.

We examined serious adverse events in the cardiac disorder/system organ class classification, and this slide summarizes the 17 events that were directed to this group. The top line is a cardiovascular death, and this was the one death mentioned earlier that occurred in a patient randomized to placebo. In the next line, we show four

patients randomized to Qnexa who had nonfatal myocardial infarctions.

In the next line, it shows four patients randomized to placebo who required emergency revascularizations, and in all four patients, these were emergent revascularizations. In three cases, a stent was placed, and in a fourth, coronary artery bypass graft was conducted.

The rest of the cases below those lines, as you can see, distribute in different categories such that the total of this category were nine subjects randomized to placebo who had a serious adverse event and eight subjects on Qnexa. Because there were one and a half times as many patients in this analysis in the Qnexa group -- as you can see at the top, more than 2500 patients on Qnexa and 1700 on placebo -- the relative risk was .60 Qnexa to placebo, with the confidence interval ranging from .23 to 1.54.

We looked at the serious cardiac adverse events in several different groupings. One grouping, called MACE, which stands for the major adverse cardiac events, included cardiovascular death,

myocardial infarction, stroke, coronary revascularization, unstable angina, and congestive heart failure.

In a second grouping, which is the one I just showed, it was the cardiac disorder/system organ class serious adverse events. These would be serious adverse events that mapped to the cardiac disorders grouping using the MedDRA classification system.

Then finally, we cast a wider net and included all cardiovascular and neurovascular serious adverse events. These included any serious adverse event from the cardiac disorder/system organ class, vascular disorder/system organ class, general disorder/preferred term of chest pain, respiratory system organ class, preferred term of pulmonary embolus, neurological system organ class, preferred terms that included stroke, TIA, and syncope.

When we looked at these three ways to classify the serious adverse events, we see that in the most narrow, which would be MACE, there were eight events on placebo, six on Qnexa, with the relative risk of .50. In the cardiac disorders SOC, which was

recently reviewed, that was a relative risk of .60.

In the broadest net, which would be the cardiovascular/neurovascular serious adverse events, there were a total of 40 events in the investigational program. And by the classification, there were 22 on placebo and 18 on Qnexa. The relative risk was .55, and the 95 percent confidence interval ranged from .30 to 1.02.

Looking at this further, we examined five potential ways to classify the serious adverse events, ranging from the most conservative to the most broadly inclusive. If one looks at the cardiac ischemia serious adverse events, which is included in the briefing document, you can see that there were six on placebo, five on Qnexa. And then as you go down the list, you get to the all-inclusive cardiovascular/ neurovascular serious adverse event class, showing the 40 events as previously described.

Importantly, the relative risk in all of these classification systems ranges between .50 and .60. The confidence intervals range from a high of 0.17 to 1.84 in the most restrictive system, to 0.30

to 1.02 in the most inclusive classification system.

Next we looked at the effect of Qnexa on laboratory parameters. Allow me to summarize those outcomes here.

First, there was no effect of Qnexa on any hematologic parameter that would be part of a standard hemogram. We looked at liver function, and there was an overall mean reduction in transaminase levels. There was no difference among the groups in the incidence of significant elevation, defined as three times elevation in transaminase levels.

We examined serum potassium level and noted a small reduction in some patients, which was driven by the co-administration of non-potassium-sparing diuretics. We also examined serum bicarbonate, and there was a mean reduction overall, ranging from .3 to 1.3 milliequivalents per liter, depending on the treatment arm. There were two adverse events of metabolic acidosis reported, one at the mid dose and one at the top dose of Qnexa.

We would like to discuss further the serum bicarbonate lowering since this is one of the key

questions raised by the division.

Here we see the persistence of bicarbonate lowering to less than 21 milliequivalents per liter, or persistent lowering to below 17 milliequivalents per liter, by treatment group. You can see at the top that in the placebo-treated subjects, 2.3 percent had a lowering to below 21, versus 11.5 percent of subjects at the top dose of Qnexa. If one examines persistent lowering to less than 17 milliequivalents per liter, that difference was .1 percent on placebo and .7 percent on the top dose of Qnexa.

We also examined the incidence of a lowering serum bicarbonate to less than 17 milliequivalents per liter, which would be clinically significant, at any time during the study to see if the lowering truly persisted. As you can see from this slide, more subjects on mid dose and top dose of Qnexa had a lowering at any point in study of a bicarbonate to 17 milliequivalents per liter or lower.

However, if one examines how often this occurred consecutively, you can see that it occurred in most subjects just once, in occasional subjects

twice, and in no subjects was it present on three or more consecutive occasions. Keep in mind that the serum bicarbonate was measured at beginning of study, at end of study, and five times in between. So the fact that lowering occurred on no more than two consecutive occasions suggests that the lowering of serum bicarbonate to this level for most subjects is mostly transient.

We also examined the time course of the lowering of the serum bicarbonate. And this slide shows, in all subjects who had a value below 21 at any time after randomization, the time course of the bicarbonate excursion.

As you can see, at baseline in these subjects, the serum bicarbonate was relatively normal, and the nadir of their level occurred between four and eight weeks. In most subjects, without any change to the administration of study drug, there was a correction of bicarbonate on its own, in most cases toward normal, as you can see by week 56.

So in summary of the general and cardiovascular safety, common adverse events with

Qnexa were consistent with known side effects of the two approved agents. There was higher study discontinuation due to adverse events on Qnexa, but there was also higher overall study completion on Qnexa.

Persistent serum bicarbonate reduction to less than 17 milliequivalents per liter was infrequent. It occurred in less than 1 percent on the top dose of Qnexa, and as I showed, in many patients it was transient and corrected on its own.

Qnexa was associated with a 1.6 beat-per-minute increase in heart rate, and a 3.1 millimeter decrease -- that's placebo-subtracted -- in systolic blood pressure at the top dose. But elevated heart rate outliers also showed a simultaneous decrease in their blood pressure and no change in their rate-pressure product.

The incidence of serious cardiac adverse events was similar between Qnexa and placebo, and I've shown the mid case scenario, with a relative risk of .60 and a confidence interval of .23 to 1.54.

At this point, I'd like to turn the program

over to Dr. Gadde.

DR. GADDE: Good morning, panel members and the FDA staff. My name is Kishore Gadde. I am an obesity researcher at Duke University Medical Center, with a particular focus on developing new drugs. I'm a board-certified psychiatrist with additional training and research at the NIMH.

I have received research funding from Vivus, Incorporated as an investigator, but I have not been a paid consultant for any company for the last two years, and I do not own stock in Vivus. This sponsor is well aware that I do own substantial stock in Orexigen Therapeutics, which is a company that is also developing obesity products.

I have been very closely involved with the Qnexa development program, starting with the 200-subject proof of concept study done entirely at our site. And in the later part of the Qnexa development, I have served as a lead investigator of the phase 3 trials. So in that capacity, I'll be presenting the neuropsychiatric safety data.

As noted by the upcoming presentation of the

FDA, one of the strengths of the Qnexa program is that the criteria for exclusion of patients with psychiatric disorders are not highly restrictive. Only 4.1 percent of patients failed due to depression exclusion criteria.

Twenty-eight percent of patients with psychiatric disorders -- of the patients entering the clinical trials, in the one-year clinical trials, 28 percent had a history of psychiatric disorders. Twenty-one percent had a history of depression, and 15 percent were taking antidepressants at study entry. Patients with suicidal ideation history were allowed in these studies as long as the suicidal ideation was not accompanied by an intention to act on the ideation, and 4 percent of the study participants had a history of suicidal ideation.

Because of concerns about anti-obesity drugs that are centrally acting, close attention has been paid to psychiatric assessment in the Qnexa program, in several different ways, adverse event collection and assessment, and for assessment of depression, the PHQ-9, a nine-item questionnaire, has been

administered at every visit. And for assessment of suicidality, the Columbia Suicide Severity Rating Scale was administered, also at every visit throughout the Qnexa phase 3 program. That amounted to more than 45,000 assessments for depression and suicidality.

To give you an accurate and true picture of the estimate and incidence of adverse events, we have taken the preferred terms, such as depression, depressed mood, altered mood, mood swings, and combined them into broader categories as depression targeted medical event, or TME, subclass.

Similarly, for anxiety, we combined anxiety and irritability and agitation into the anxiety subclass. Keep in mind that irritability is actually listed in the MedDRA dictionary under general category, but we felt that it belongs here. Similarly, we combined terms such as insomnia and somnolence in the sleep disorders class.

Looking at the frequency of adverse events, you find that for sleep disorders, for anxiety and depression, you see a dose-dependent increase in the frequency of adverse events, especially with the Qnexa

top dose. Of note, the incidence of depression, TME, was not particularly increased in the mid dose of Qnexa.

Most of the patients with psychiatric adverse events continued in the program. However, a small portion of them discontinued. But you do see here an increase in the frequency in the Qnexa groups relative to placebo, particularly with the top dose.

Most of the discontinuations for psychiatric adverse events occurred in the first three months. Approximately 75 percent patients discontinued in the three months, first three months, suggesting that those patients who tolerate Qnexa in the first three months are unlikely -- are not very likely to have bothersome psychiatric adverse events in the subsequent months.

Here we are showing a breakdown of the preferred terms in the depression TME class, where the preferred term depression is the most common, and you do see a doubling of the frequency in the top dose group relative to placebo. Most of the depression adverse events were mild or moderate in severity, as

coded by the investigators.

We also assessed, as I stated earlier, depression at every visit with the PHQ-9 Self-Rated Rating Scale. And looking at the total change in the total score, you find that in all the treatment groups, there was a small decrease in the mean PHQ-9 score. And this is not surprising, because as a group, weight loss is associated with a slight improvement in mood.

There are different ways of analyzing the data for PHQ-9. One way of analyzing data is looking at the percentage of patients who had a PHQ-9 score of 10 or higher at any time, and also the percentage of patients with a PHQ-9 score of 15 or higher at any time.

For those with 10 or higher at any time, there was no difference between the groups. But when the data were analyzed for those with 15 or higher at any time, you do see an increase for the Qnexa top dose, but not for the mid dose.

Another method for analyzing the data for PHQ-9 is looking at the proportions of patients who

had worsening by one or two categories. As an example, if you start with PHQ-9 scores of 5 to 9, it's in the mild category. And then you move to 15, that's a two-category worsening. There is no difference between the groups in this analysis.

Another way of understanding the clinical significance of the depression events is looking at how many patients had to be prescribed new antidepressants during the course of the study. And there was no difference between the groups in the prescriptions for new antidepressants.

There were no serious adverse events for depression or depressed mood in the one-year trials with Qnexa. There were no hospitalizations.

I stated earlier that we assessed suicidality in a prospective manner with CSSRS, which is the Columbia Suicide Severity Rating Scale. And with these assessments, there were no cases of suicide attempts, no cases of self-injurious behavior, and no suicidal ideation with intent. And there were a few cases of suicidal ideation without intent. The numbers were 11 for placebo and 14 in the top dose.

There were three cases -- of these, there were three cases of suicidal ideation without intent that were actually reported by the investigators, one in the placebo group, one in the Qnexa low dose group, and one in the Qnexa top dose. There were no major differences in these mean scores for PHQ-9, question number 9, which is the suicide item.

So in conclusion, there is no increased risk of suicidality, as assessed by three separate methods in a prospective manner.

Now, turning on to cognitive disorders, again we have combined the preferred terms into broader categories of attention, memory impairment, language, and other cognitive disorders. You see here that there was a dose-dependent increase in the frequency of cognitive disorders with Qnexa, particularly in the areas of attention and memory impairment.

Looking at discontinuations, you find that most of the patients that develop cognitive AEs continued in the program. And after a few patients that discontinued, again there was a dose-dependent

increase in the frequency with Qnexa, particularly in the areas of attention and memory impairment.

To give you a breakdown of the severity, I'm showing here the severity in the attention subclass. You find that predominately these cases were mild or moderate in severity.

So in summary of the Qnexa neuropsychiatric safety, there was a dose-related increase in the neuropsychiatric adverse events and study discontinuations. Approximately 90 percent of neuropsychiatric adverse events were mild or moderate in severity. There were no serious adverse events and no hospitalizations related to depression, anxiety, or cognitive adverse events throughout the program.

There is no increase in the risk of suicidality, as assessed by three separate methods in a prospective manner in a population where 21 percent of the patients had a prior history of depression and 15 percent were taking antidepressants at baseline.

With that, I turn the mic back to -- I turn it over to Dr. Gideon Koren.

DR. KOREN: Thank you very much. I'm coming

to you from the University of Toronto, where 25 years ago I built a program called the Motherisk, which focused on the safety risk of drugs during pregnancy and lactation. And this is the focus of my career.

At the present time, I have 70 individuals working. It's the largest such program in the world. We collaborate with similar programs in North America. We work a lot with the FDA on many of the registries. As part of the organization of teratology information services, we are the largest partner bringing cases to advise the agency about safety.

We published over 800 peer-reviewed papers on safety of drugs in pregnancy, including in the New England Journal of Medicine, JAMA, BMJ, Lancet, and such. We published more than 15 medical books on the topic. And most importantly, we counsel every day about 200 women from Canada, the United States, and other parts of the world, and their health professionals, on safety of drugs in pregnancy.

I have no conflict of interest, financially or otherwise, with this project or with any of the proceedings, and I never worked with Vivus before. I

was asked to come here specifically to address the fetal safety of the medication.

Naturally, when a drug aim at women of reproductive age, we should look what will happen to the unborn because 50 percent of all pregnancies in North America are unplanned. Unplanned does not mean unwanted, but it means that a lot of babies will be exposed to a drug. I thought it's a high percentage, but I can tell you, I have four kids. Fifty percent. That's correct.

[Laughter.]

DR. KOREN: So I'll go walk you through the process we do in Motherisk in our work, which is similar to the process that will lead me to advise a woman whether it's safe to take topiramate in pregnancy.

Lucky enough, topiramate was introduced 14 years ago, so by now, large number of women were exposed to the drug. As it happens, unplanned pregnancy, and indeed, physicians often may want a woman to be on a drug like topiramate for epilepsy because they may deem it important for them.

So as of 2010, there are four registries reported from different parts of the world, one from Israel, one from the U.K., one the North American registry, and one from Australia. That per se is reassuring because it's not just one area; it's really the world experience. In Motherisk, we trained physicians from 35 countries, who went back and started such systems. And we of course communicate when a woman come with a drug of interest.

So what you see here is the numbers. The numbers are not huge, but altogether, about 400 reported in the literature by now. And as you can see, there are major malformations, which is what we, of course, are interested in more than anything else. The rate is about 3.7 percent among those studies. This is well within what happens spontaneously in the population.

If you go now in Washington to an obstetric unit, between 3 and 5 percent of babies are born with malformations. So without knowing too much, it's clear that this number is not high. It's well within what described.

Now, how can you compare it to women not exposed? Different places compare it in different ways. But the real, true way to compare it is to women with epilepsy which are not treated, and not just with other women. You want to have a control group which is as close to the group you're interested in.

So it so happened that Motherisk has done that. We published, in Drug Safety in 204, all the world experience with women with epilepsy who did not receive any drug. After that, for the sake of this presentation, two more studies were added to that experience that reported in 206 and 208; altogether, 710 women with epilepsy that did not take any medication during the pregnancy in question. And look here. This is the key point. The overall malformation rate was 3.4 percent, again, well within the range.

As an editorial comment, for many years women were told, if you have epilepsy, you have a more chance of malformations. These studies actually refuted that particular myth. And as you can see,

it's very, very much within what one expect.

So let's combine now these two pieces of information. And as you can see, this is the topiramate, and this is the untreated epilepsy. The rates are relatively similar, and the relative risk, which is how much one is more than the other, is really sitting on one.

For me, as someone who has to counsel women, there is another important piece of information here. The 95 confidence interval is very tight. If the upper confidence interval would have gone to, say, 8 or 10, I would know that the data is very -- is all over the place, as we say. But that's not the case. Actually, it's quite tight, which suggests that although the numbers are still not very large, no signal has shown itself in the last 14 years.

There is another element of importance when we have to counsel a woman tomorrow on topiramate who happened to be pregnant or planned to be pregnant, and that is that the new product under focus of discussion today have lower dose of topiramate than what was given to epileptic women. So per kilo, the woman sees

less of the drug.

Second, the new product is aimed at women with obesity. They are much larger. So they are much larger, and they receive lower dose. So per kilo body weight, they receive less than half of what women with typically in epilepsy receive. So this is another factor of safety. Truly, the numbers are not huge. However, the dose we are discussing today is much smaller than what the women on topiramate received in the last 14 years.

There are other sources of information we have to consider in our work. One is the spontaneous reporting system of the FDA, whereby practitioners from all over North America and elsewhere are invited to report on adverse events. And over the last 14 years, 23 cases of U.S.-based women who took topiramate in the first trimester had malformed kids. You expect it, because at the same time, estimated 5 million women of reproductive age received topiramate. So you expect some of them to have malformations.

The question is whether those malformations are very unique. For example, if all 23 women had

kids without ears, this must be something. But that's not the case. As a matter of fact, the range of malformations in those 23 cases is what you expect in the general population. So there is no clear signal here.

The other source are the animal studies. You know that any new drug as topiramate submitted to the agency have to show standardized studies in animals. And of course, the animal studies with topiramate showed oral cleft. I should tell you, and my colleague teratologist here can attest to it, mice are very sensitive to oral cleft and we see a lot of clefting among mice, their ribs, vertebrae. And again, I want to show you that does not fit what the FDA spontaneous cases show.

Put together, if a woman come to me -- and indeed, two weeks ago I saw in Motherisk a woman with topiramate -- I will reassure her that if she took the drug into pregnancy, she is not likely to have an increased risk for malformations. Of course, if her physician writes to me and want to know whether she can continue, I will share with him or her the data

that I described to you now.

Now, during the studies with the new product, the program was a large program, and a total of 34 women conceived while on the program. This information here, too, again reassuring. Thirteen women end up with a live birth after taking the Qnexa. None of these kids had a malformation, serving again to remind you this is a smaller dose in a much larger BMI, obese women. Now, this is not a large number. But it again strengthening everything I told you in the last 7 or 10 minutes.

To balance everything we said today, we have Imast (ph) as someone whose career is in this field to remind all of us that obesity itself is teratogenic. Obesity, being with obesity BMI above 30, increase malformation rates. The most clear today is the neural tube defects, proven by repeated studies. We analyzed that data and meta-analyzed it, too. There is a more than twofold risk for spina bifida in women who are obese.

But there are many other risks involved in pregnancy for obesity itself -- not the drugs, the

obesity -- such as hypertension, the need for Cesarean section, gestational diabetes, to mention a few. So we are not talking here neutral background. We are talking very large risks, reproductive risks, to do with overweight and obesity, which have to be considered.

In summary, if you were on topiramate today and came to see us in Motherisk, after the analysis I showed you, the systemic review of the existing data today do not suggest an increased risk of major malformations with topiramate in pregnant woman when compared to untreated epilepsy, for the reasons I explained to you. The pattern of reported malformation in the spontaneous system is consistent with what you expect. There was no excess of any particular malformation.

The sponsor is proposing a prospective pregnancy exposure registry, where I very strongly support. We should continue to collect that data in order to be able, with larger numbers, to see a signal if such a signal, of course, occurs.

Of course, not including in my slide, I

believe that we should have a very proactive program to advise women, educate women, and to ensure a pregnancy protection program that, as far as one can, to prevent pregnancy while on that particular combination on drugs. Thank you.

DR. GESUNDHEIT: Thank you, Dr. Koren.

We would like to summarize the results from the clinical program and also talk about the risk mitigation program that we would like to put into place pending approval. We'll discuss, then, five separate areas, and each of these corresponds to one of the areas of interest that have been posed by the division.

For psychiatric side effects, our summary is that these effects were more frequent on Qnexa, but were typically mild and not associated with an increased use of antidepressant medications. They were identifiable early, and they were associated with a dropout rate that was greater than placebo, but overall, was relatively low. There was no increased risk of suicidality, as Dr. Gadde reviewed.

In our proposed labeling, we propose that we

state that patients and their families should be alert for the emergence or worsening of depression, anxiety, suicidal thoughts or behavior, and any unusual changes in mood or behavior. And we will disseminate this information through a medication guide to physicians, pharmacists, and patients, and also will advise physicians to include screening instruments, such as the PHQ-2, which is a shorter version of the instrument that Dr. Gadde discussed, for periodic assessment of patients.

For cognitive side effects, the summary is that cognitive side effects were more frequent on Qnexa, but were reversible and mostly mild. These events also were identifiable early and associated with a low dropout rate of about 2 percent that was greater than placebo.

In our labeling, we propose very similar to what's in the current topiramate labeling, that Qnexa may adversely affect cognitive function such as attention and memory. And we will advise patients that they should use caution when driving a car or operating heavy machinery until they know how Qnexa

affects them. We will disseminate this information as well through the medication guide and other communication materials.

For metabolic acidosis, our summary is that persistent serum bicarbonate to levels below 17 milliequivalents did occur with greater frequency with Qnexa, but it was relatively infrequent, with less than 1 percent of subjects at top dose.

The proposed labeling would advise physicians that bicarbonate decrements are present, usually mild, an average decrease of about 1 milliequivalent per liter at the top dose, and that less than 1 percent of patients, about .7 percent, can experience persistent decrements of bicarbonate to below 17.

As in the current topiramate labeling, we would advise physicians about conditions or therapies that, by themselves, may predispose to metabolic acidosis and that could be additive to the bicarbonate-lowering effects of topiramate. And we would advocate baseline and periodic measurements of serum bicarbonate in such predisposed patients, and

that physicians should consider dose reduction or discontinuation of Qnexa if it's clinically appropriate due to lowering of serum bicarbonate. We would disseminate this information again in the medication guide, and we're interested in looking at the long-term clinical effects as part of a phase 4 program.

For pregnancy, our summary is that the risk of human malformations at topiramate doses used in epilepsy, which is up to 400 milligrams per day -- and just to reflect on Dr. Koren's comment, our top dose is less than one-fourth of that dose, not correcting for body mass index -- but it has not been demonstrated. And there is no evidence of malformations with Qnexa per se.

Our proposed labeling, however, would be that weight loss during pregnancy is not recommended, and we embrace the majority of the recommendations from the maternal health team that have been included in your briefing document. Qnexa should not be used if a woman is pregnant or attempting to become pregnant.

In terms of risk management, we will make these materials available in the medication guide. We will aggressively advocate for contraception and pregnancy prevention education. And we will begin a pregnancy exposure registry, hopefully to include potentially other sponsors of pregnancy -- of weight-reducing drugs.

For heart rate, our summary there is that Qnexa was associated with a 1.6 beat per minute increase in heart rate. But along with that, there was a 3.1 millimeter decrease in systolic blood pressure at the top dose. As we showed, elevated heart rate outliers also showed a decrease in their blood pressure, which we believe mitigates that effect. There was no increase in clinically significant arrhythmia. In the clinical trials, we will mention the effects on heart rate in the proposed labeling, and we will distribute this information in the medication guide.

Finally, we believe strongly that Qnexa is one piece of a much larger effort, that patients who benefit from Qnexa will do so only if there is an

integrated program that advocates physical activity, healthy eating and nutrition, and behavior modification as long-term measures that can help patients lower their weight and sustain their weight at a lower label. It will be a major emphasis of our program to educate patients and physicians about the need to engage in such a comprehensive program, of which Qnexa is only one small part.

We also plan to engage in an outcomes trial. The exact details will be decided with the division, but the goal of the trial will be to look at a composite endpoint of myocardial infarction, stroke, and other serious events shown here so that one can gauge, in real clinical practice, what the effect is of Qnexa compared with the control group on the potential risks or potential benefits to these clinical endpoints.

So in summary, Qnexa is comprised of low doses of two approved drugs, each with millions of patient years of experience. The safety risks associated with Qnexa are known and are consistent with the properties of these two agents. As mentioned

earlier, we did not observe any surprises during the clinical investigational program.

In terms of efficacy, there is no pharmacotherapy that currently attains 10 percent weight loss, which would be in accordance with the NIH guideline recommendations. However, with Qnexa, in conjunction with diet and an exercise program, we see in most patients a 10 percent or greater weight loss, which is accompanied by clinically meaningful improvements in weight-related comorbidities.

To review the effect on weight loss, this slide shows a cumulative distribution of patients losing weight on Qnexa at the top dose. This is analysis of Qnexa completers. These are patients who succeeded and remained on study for one year. And these data here are from patients who were on study 302, in which the patients had morbid obesity. The mean BMI in that study was 42 kilograms per meters square.

The way to orient yourself to this slide is to imagine that patients are lined up on the X axis according to the percentage of weight change they had

from baseline, and that we did a cumulative summary from left to right of those patients. What you can see is that about 15 percent of patients lost 15 percent or more of their weight on Qnexa top dose.

Again, this would be about 35 to 40 pounds of weight in patients with this degree of body mass index who stayed on therapy for one year. In fact, if you look at the percentage of patients losing 20 percent of weight, nearly 30 percent of patients lost 20 percent of weight among these patients with morbid obesity who completed the trial.

These levels of weight loss are unprecedented. They're similar to the levels of weight loss, 15 percent or greater, that one observes with some types of bariatric surgery.

When we look at other effects beyond weight loss, one sees that Qnexa has global effects that can improve the health of these patients. When you look at waist circumference, there is a significant reduction. Systolic and diastolic blood pressure go down significantly. There are changes, favorable ones, to inflammatory markers. And the whole host of

measurements of insulin resistance all move favorably in patients treated with Qnexa.

In addition, when we look at quality of life measures, either using the SF-36 instrument that Dr. Day illustrated or the impact of weight on quality of life, there's clearly a significant improvement in patients' self-perception of their quality of life. The changes are greater in the top dose, shown on the right, but these changes on the global indices were also observed on the mid dose of Qnexa.

Importantly, we looked at progression to type 2 diabetes in the OB-303 study. These subjects were not diabetic, but in most cases had impaired fasting glucose at study entry. What we see is that in the patients treated with placebo, despite adhering to a diet and exercise program, there was a 20 percent progression in one year to a biochemical diagnosis of diabetes, as defined below.

In the patients randomized to Qnexa top dose, there was a 46 percent reduction in the incidence of diabetes relative to placebo. The difference in the top dose of Qnexa in terms of

reduction was statistically significant, and it bordered significance at the mid dose, as shown on the right side panel.

So in overall summary, we believe there is currently a treatment gap, as mentioned by Dr. Aronne, in the management of obesity. Current pharmacotherapy, as shown on the left-hand side, can achieve weight loss that is modest. Bariatric surgery achieves much more dramatic weight loss, as shown on the right-hand side.

We feel that Qnexa can be an important new therapy that can obviate the need for surgery in many patients, bring significant benefits, and fill an important treatment gap that currently exists in the medical management of obesity. Thank you.

DR. BURMAN: Thank you very much.

The floor is now open for questions from the committee.

Dr. Weide?

DR. WEIDE: Thank you. I have several questions. The first would be in slide -- I guess it's 19, which was your OB-201. I don't know if we

can put that back up.

Could you tell us what the doses are for the individual components there?

DR. ARONNE: Yes. The dose of Qnexa used in this study is listed in the top. It's 15 milligrams of phentermine and 100 milligrams of topiramate. And this was compared to the monotherapy doses, 15 milligrams phentermine, 100 milligrams topiramate, and placebo.

DR. WEIDE: Okay. And did you do any dose response curves? Because, as you say, both of these drugs are available, and physicians are currently using these drugs in combination for weight loss. And so there's an ability to use 30 milligrams with 400 currently. So why did you choose the dosage you did?

DR. ARONNE: Yes. Fair question. The selection of dose was fairly challenging. As you allude, there's a number of papers at that time the outline the weight loss properties of especially topiramate. I think Dr. Bray's studies were very good at establishing the dose response.

The dose selection was initially based on

assessment of the tolerability of the monotherapy relative to the weight loss needs. It was seen in the published papers on topiramate that 200 seemed to be about the peak dose for weight loss. It was associated with 8 to 9 percent weight loss.

One hundred milligrams in the published papers at that time was deemed a reasonably tolerated dose, but the weight loss was fairly marginal. So the hypothesis was, if we throw phentermine in there with topiramate at a lower dose, the fact that we're combining a number of different mechanisms, we may be able to achieve better weight loss with a more tolerable dose. So essentially, the results of that study kind of established that hypothesis.

I think it's important to note as well -- oh, sorry, I'm pressing the wrong button. I think it's important to note what's been listed here is kind of a summary of the literature that's available, not only for weight loss with topiramate, but also some of the antihypertensive/antidiabetic studies that have been conducted, a number of studies, mostly through Johnson & Johnson.

But the basis of the assessment of the literature at that time kind of established that if we could get a dose of 100 that was tolerable, that would be a good starting dose, and that essentially set the ceiling.

DR. WEIDE: I have two other quick questions.

When they stopped, did they regain the weight? That happens with most of the medications.

DR. ARONNE: Yes. We didn't assess that in 2001, but we have assessed that in our phase 3 program.

If I could have the slide of weight regained.

We didn't initially plan to assess this in the study, and actually, in a retrospective manner, we came up with a way to kind of understand this. So the assessment was made in subjects that -- as I mentioned in my presentation, about 5 to 9 percent of subjects went off drug but stayed in the study. So we took that group of subjects. We identified subjects that had at least 5 percent weight loss, so we have kind of

a threshold of weight loss to establish a weight regain. And in this group of subjects, we saw average weight loss of about 10.9 percent. And that weight loss varied among subjects, but it was at least 5 percent overall.

What you see is that subjects regained, over the course of remaining in the study, up to about 4 percent of that 10 percent, or about 40 percent regain after going off treatment.

DR. WEIDE: My last question, and then I'll let other people talk.

With the concern about the bicarb lowering, and I know it's not very common, a lot of people who are overweight are on multiple medications to lose weight, one of which is metformin. A lot of them have diabetes. A common drug is metformin.

Are you concerned or have you looked at metformin in these patients so that when there -- the possible increased risk of lactic acidosis in these patients?

DR. GESUNDHEIT: Yes. That was a concern, and I'll show you data. We did have the benefit of

having quite a few patients on metformin in the study that was enriched with diabetic subjects. That would be the 303 study.

What you can see here, if you look at the left-hand side, it's pretty much reproducing what we showed earlier on the left-hand side. These were the patients not on metformin, which would then be a comparator group. And you can see at the level of bicarbonate lowering to less than 21, which is the top line, or lowering to less than 17, that we did see rates, as we mentioned in the core presentation, of patients who had a lowered bicarbonate.

We then looked at -- well, let's see. Does metformin make that worse? Does it either lower their bicarb more or have any other adverse events on the acid/base balance? And so on the right-hand side, you see the experience in a total of about 450 subjects who were on metformin and were in the program. And what you can see is the rates of developing serious bicarbonate lowering, either to less than 21 or less than 17, are virtually the same -- let me just use my pointer -- so were virtually the same, 11.4 versus

11.3, .9 at the more severe level versus .7.

So it did not appear that there was any additive effect or interaction with metformin and the Qnexa in terms of the bicarbonate issue.

DR. BURMAN: Thank you. We have about 10 people who want to ask questions, and we have about 20 minutes. So please keep your questions and answers succinct.

Dr. Veltri.

DR. VELTRI: Yes. Two quick questions, one on efficacy, one on safety.

In regards to the efficacy, all of these trials were parallel designed. Yet the recommendation from a regimen perspective is kind of a forced titration based on response. So does the sponsor have or is there any plan to actually look at a dose titration as opposed to just obviously to emulate what the recommendations of the regimen would be?

Secondly, you didn't touch upon it, but in your briefing document, table 30, you talk about syncope. And if you look at syncope in this population, there were 15 episodes of syncope, or loss

of consciousness, on drug versus 4 on placebo. And they're mostly in the high dose group, 10 of the 15.

My question is, is there any information from the clinical study on when these occurred? Were they early? Have you looked at orthostasis changes to kind of get a gleam of this? And this is important, especially since there were small numbers of patients who had atherosclerotic disease. And that could be -- syncope could be more serious in patients with established atherosclerosis.

DR. GESUNDHEIT: For the first question, the program did randomize patients in parallel arms to different doses of the Qnexa. However, we've done a considerable amount of work looking at the dose response relationship, and that shows a clear dose response relationship. And there were also patients who were kept at one level but didn't tolerate it, for instance, and were lowered to a different level.

But in terms of the actual algorithm, it's based more on sort of a practical sense of what would be a realistic way to proceed, with the goal that we would want each patient to be on the lowest effective

dose.

So the algorithm is a practical one, which aims to put patients on the low -- well, the mid dose, which is the recommended dose. And only if they do not achieve their excepted -- or the target weight loss, would you then go to the higher dose. It's a practical regimen based on the experience from the parallel design study, as you point out.

We did titrate patients up to that dose just to make sure that that's clear. There was a four-week period of titration where even if a patient was at the top dose by randomization, they needed to be at lower doses in a blinded manner at a one-week interval until they got up to the top dose. But you're correct. We didn't keep people on long periods of time on one dose and then systemically increase them to the higher level.

Let me show data on syncope because there were more on drug, but of course we had more patients treated with drug. What this shows here are syncope-related treatment-emergent adverse events. And you can see that as a percent on placebo, there were .3

percent, whereas on Qnexa top dose, it was .4. Maybe the extra events that you're alluding to are because there were some at the mid dose as well as the top dose.

In terms of serious adverse events, syncope events that required hospitalization or were deemed to be serious, we basically had one on placebo, and we had one on Qnexa top dose, so it looked balanced.

But there is a blood pressure-lowering effect, and it is part of our mitigation program to advise physicians to check blood pressure. I think the suggestion that they should look at orthostatic changes is an excellent one, and that's something we can include in the risk mitigation program.

DR. BURMAN: Thank you.

Dr. Proschan?

DR. PROSCHAN: Yes. On slide CC-59, it shows -- yes, it shows that even in the placebo group, there's a big drop at four weeks. And I'm wondering if the entry criteria of the trial would cause some artificially high values at baseline.

DR. GESUNDHEIT: There may be some selection

bias because in order to get into this analysis at all, you had to have a bicarb below 21 at some point. But it is curious why did even the placebo patients show some degree of -- it was less lowering than the treated patients at four weeks.

It's not clear to us, but it actually didn't go outside the normal range. In our lab, the normal range is 21 to 29, so at least the mean value at that time point for the placebo patients was okay. And just as the others tended to correct over time, the mean values tended to go higher as time went on.

DR. PROSCHAN: And just one more. On CC-51 -- yes, I'm not sure how to interpret this because this is inpatients whose heart rate went above 100, which is going to be a different group of patients in the Qnexa arm than the placebo arm. Because if the drug increases the heart rate, then the group that has heart rate over 100, it may not necessarily be comparable in the two arms. So that makes it kind of difficult to interpret.

DR. GESUNDHEIT: Well, I see your point. But our view is that we wanted to, in this analysis,

look at the patients who clearly would be at greatest risk. If a patient has a persistent tachycardia, that would seem to be a patient that might be at higher cardiovascular risk.

We found that, actually those occurred even in the placebo patients. There were patients in placebo, the 10 or fewer, but there were 10 patients in placebo who had a heart rate of 100 or greater on two or more occasions.

The purpose of this analysis was to see if you have these heart rate outliers, the most severe heart rate outliers, in them, do you even in them see a lowering of blood pressure. And we did see that with Qnexa.

So it's protective in that sense, that if you get tachycardia with Qnexa, because of the blood pressure lowering effect that's built into the drug, you actually see a lowering of the rate-pressure product, suggesting less risk per se in a patient who gets tachycardia. I don't want to claim less risk. We're just saying that it looks comparable, and certainly no increase in risk in the patients who have

tachycardia with Qnexa.

DR. BURMAN: Thank you. Just a comment.

With regard to the lowering bicarb, even in the placebo group, obviously decreased calories, fasting to any degree, will elevate free fatty acids and lower the bicarb.

So did you measure free fatty acids?

DR. GESUNDHEIT: No. But along those lines, we did look at ketones via the anion gap because we also had that concern. And interestingly, because patients were on this LEARN diet, which was meant to be a balanced diet, not a low-carbohydrate diet, and meant to decrease caloric intake by about 500 calories per day.

The anion gap, as you went time period over time period in the Qnexa arms, did not change. So if there was any ketogenesis, it wasn't significant enough to alter the anion gap.

DR. BURMAN: Thank you.

Dr. Heckbert.

DR. HECKBERT: Yes. I have two questions, but they're brief, for Dr. Gadde.

Dr. Day said that some patients used psychiatric medications mostly as SSRIs. And my question was what proportion of patients used those, used antidepressant medications, and did they stay on their meds throughout the study?

Then just quickly, the second question, which is also for Dr. Gadde, in slide CC-67, you indicated that the psychiatric adverse effects were mostly -- that led to discontinuation mostly occurred in the first three months.

I wondered whether the cognitive adverse effects -- attention, memory, et cetera -- whether those were continued throughout the study, or were they also limited mostly, in terms of discontinuation, to the first three months?

DR. GADDE: Do we have a slide for the cognitive adverse events? So firstly, psychiatric adverse events such as depression, anxiety, this slide clearly shows that most of the adverse events are happening in the first three months.

We do actually have a side for -- yes. Just as an example, the attention subclass where you find

again that with Qnexa top dose, there was an increase in the number of dropouts early on in treatment, which sort of plateaus later on. And I believe this is true for the other cognitive adverse events as well.

DR. HECKBERT: Is that first event report or is that time course of dropouts? It looks like it's event reports. So I'm wondering, did people continue to have these symptoms throughout the whole time they were on the drug?

DR. GADDE: One way of looking at it is the mean duration. And it's about 24 days for the top dose, and about 20 days for the mid dose. And the time of onset for the first onset is 20 days for the top dose, about the same as with the placebo.

Most of the events resolved, and only about .9 percent discontinued the study drug in the top dose, although it's a greater percentage compared to placebo. So most did. And when the drug was discontinued, in most cases the adverse event resolved fairly quickly.

DR. BURMAN: Thank you.

Dr. Capuzzi?

DR. CAPUZZI: Yes. Just two questions.

You're proposing using a combination of two drugs at once. I just want to know, in terms of screening patients for their underlying cause for the obesity and you're going to be using phentermine, just what have you done to eliminate the possibility of subclinical coronary artery disease or a serious life-threatening rhythm disorder?

Also, did you do anything besides a TSH for ruling out the subclinical hypothyroidism?

DR. GESUNDHEIT: In our program, we did do entry EKGs, and patients were admitted with a coronary history. They had to not have had a major event in the prior six months. But we included patients who had had major events, including MIs, beyond the six-month -- longer than six months, into the trial program.

We did EKGs at entry. We did EKGs at exit. We did vital signs 15 times over the course of the year to look for changes in rhythm that would be obvious in vital signs, et cetera.

Did you want to ask -- did you have another

thought on that? So that would be for what we saw in terms of the cardiac.

For TSH, we think there is the possibility of subclinical hypothyroidism with severe weight loss. Overall, though, we looked before and at study exit at TSHs, and there were very, very few outliers. And I think what you're going to tell me is that TSH could be in the normal range in some patients with clinical hypothyroidism.

DR. CAPUZZI: Well, it not only can't be, you could be at the high part of TSH at 4 and have a low free T3 --

DR. GESUNDHEIT: Yes.

DR. CAPUZZI: -- and/or a low free T4, or both.

DR. GESUNDHEIT: Yes. Well, our label actually -- our proposed label mentions that as a possibility, and that for patients complaining of fatigue, et cetera, especially in that early period of more profound weight loss, that thyroid function should be rechecked if patients complain of those symptoms at that time.

But again, when we looked at the TSHs and the free T4s that were seen in the program, there were very few abnormalities in free T4 and very few alterations outside of the normal range for the TSH.

DR. BURMAN: Thank you. Just a point of clarification. Speaking as a thyroidologist, if the TSH is normal -- the definition of subclinical hypothyroidism is a TSH that's elevated with a normal free T4 and T3. It's true, if you fast, the TSH can go into the normal range. But at baseline, if it's elevated -- if it's normal, they're not hypothyroid unless medications are on it.

Dr. Kaul?

DR. KAUL: Thank you. While I ask my first question, can you also pull up slide 30, forward by slide 21?

Do you have any data on a time course of heart rate and blood pressure effects? I want to make sure that you captured the maximum effect on these variables. Did you have any pilot study where you do a continuous monitoring of heart rate and blood pressure? Since most of the weight loss was up front.

DR. ARONNE: So we do have a time course on blood pressure. The slide that was previously up -- could I get the first slide he requested? So I'm trying to relate the blood pressure question to the BMI slide that you asked for.

DR. KAUL: No, no. I just want to make sure. How frequently did you measure heart rate and blood pressure?

DR. ARONNE: Okay. So the vitals were measured at every visit.

If I could have the time course of blood pressure change.

So as you can see on our OB-303 study, the assessment of systolic blood pressure is this example compared to placebo. The effects did occur early and were fairly consistent across time over the trial. And I think it's fair to say that the effects maintained a significant difference, although small, compared to placebo over time.

DR. KAUL: And if you were to overlay heart rate plot, it would coincide with the blood pressure drop?

DR. ARONNE: So if we look at heart rate over time in the same study, essentially the same population, again you can see that consistent and dose-related difference in heart rate -- again, a small difference, but clearly distinguished.

DR. KAUL: Okay. Slide 30, please.

The question I have is did you do a treatment effect by BMI interaction, by just visual inspection? There seems to be an overlap across the BMI for the doses.

DR. ARONNE: Okay. So the reason that we performed this analysis was to kind of appreciate if the dose relationship is stronger in a population of essentially greater obese subjects. The weight loss occurs fairly quickly in all doses. And what we learned from this analysis was that the dose relationship is stronger with a higher BMI.

DR. KAUL: But I'm not quite sure about that. By visual inspection, it doesn't seem to be the case. It's an overlap in the confidence limits.

Did you do a formal test of interaction?

DR. ARONNE: Mr. Schwiers will address our

statistical analysis.

MR. SCHWIERS: My name is Michael Schwiers. I'm employed in Medpace. It's a contract research organization that was contracted by Vivus to run the phase 3 programs. I've been a biostatistician involved in clinical trial data analysis for seven years, and was the statistician on the phase 3 studies as well as the NDA submission.

For all of the subgroup analyses that we did, including the BMI, the age, the race, formal interaction testing was performed, and in this example, it was not significant.

DR. KAUL: Okay. Slide 21, the sleep apnea slide.

Was that a weight-related phenomenon or was that related to some other factor, for example, metabolic acidosis with secondary hyperventilation? Did you measure bicarbonate levels in the groups?

DR. ARONNE: The assumption is that this is driven primarily by weight. But your point is well-taken on the mechanism of carbonic anhydrase and the bicarbonate. As presented in Dr. Gesundheit's

presentation in the core, we do see some reduction in serum bicarb, which equates -- in general, the population is still in the mean range, but it is an overall reduction compared to placebo.

DR. KAUL: But did you measure bicarbonate levels in these groups, where you showed the impact on --

DR. ARONNE: Yes. We did measure them and we did see a reduction consistent with what would be expected.

DR. KAUL: One last question, slide 96.

Do you have the same plots for the medium dose and the low dose? I want to convince myself that you get a greater bang for the higher dose without the safety tradeoff.

DR. GESUNDHEIT: We do. So while those are coming up, the -- okay. This is coming up. Thank you.

This plot is actually slightly different because the first plot I showed was only from the 302 study, which was the patients with greater degrees of obesity. This is now the mix of both 302 and 303, but

it's still the patients who completed therapy.

You can see that the purple line is the top dose, blue is the mid dose, and then the green is from the -- the green plot is because patients only in the 302 study had that low dose. But you can see that there is a dose response relationship, at least to my eye, at these doses, with the accumulation of patients at that level.

If you take important threshold levels like 5 and 10 percent, just to point those out, if you go to the 10 percent level, which we show here, you can see that at the green, which is the low dose, about 30 percent hit that level. At the blue, it's about 50 percent. And if you go up to the purple line -- I don't know if I have this linear -- it's about 70 percent.

Now, this is a favorable way to interpret it because this is looking at patients who complete therapy. But nevertheless, it shows a nice dose response relationship, and is part of the reason we would like to go forward, and have applied to the agency to have all three doses approved because that

would allow individualization of therapy along this line.

DR. BURMAN: Thank you. We have four minutes.

Dr. Thomas, do you have a quick question?

DR. THOMAS: A lot of questions, but I'll just ask one very quick one.

The issue with contraception, many of the women who got pregnant were on oral contraceptives. And I know that there's an alteration of the oral contraceptive effect in terms of clearance of estrogen. Was the reason that these women got pregnant because of that, or because there's an issue of attention or concentration where they failed to take their contraceptive? Or third, many women with obesity -- and they do have some data -- have menstrual irregularities and think that they can't get pregnant. So I'd like to have an idea of why the pregnancies occurred in spite of stringent efforts to prevent them.

DR. ARONNE: You are correct. We did have stringent efforts, correct, but nevertheless we did

see some pregnancies. I think the short answer to your question is a mixture of all of the above. Women were required to be on two forms of contraceptive in the trial, and women did report that they were using those contraceptives. I think it was a little less of half of the women that were pregnant were using oral contraceptives, and the other half using barrier and spermaticide type of approaches.

But we did not confirm compliance per se with some biochemical measure for contraception, so I can't specifically answer your question whether or not the contraceptive failed. Our drug interaction study did suggest a slight decrease in the AUC of estrogen, and this information has been included in the label and will be part of the education for use of oral contraceptives.

DR. BURMAN: Thank you.

We will now take a 15-minute break. We will get to the remaining questions after lunch. There's a separate time.

Panel members, please remember that there should be no discussion of the meeting topic during

the break amongst yourselves or with any member of the audience. We will resume at 10:30.

(Whereupon, a recess was taken.)

DR. BURMAN: We will now proceed with our presentation from the FDA. I would like to remind public observers in this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Dr. Roberts.

DR. ROBERTS: Good morning, Chairman Burman, members of the committee. Today I will be presenting the division's perspectives on the results from the phentermine/topiramate clinical development program.

First, I will briefly summarize the phentermine/topiramate efficacy findings with regard to the weight management indication. I will then speak to the specific safety concerns that are the focus of this advisory committee, specifically, psychiatric adverse events including suicidality, neurocognitive adverse events, cardiovascular safety, incidence of metabolic acidosis, and teratogenicity

concerns.

Phentermine/topiramate was developed under the 2007 draft FDA guidance for developing products for weight management, which recommends that the efficacy and safety of a fixed-dose combination such as phentermine/topiramate be compared to its components first before determining its efficacy against placebo. No minimum difference in weight loss between fixed dose and its components has been defined.

As a reminder, study OB-301 was a factorial design study. Adults with a BMI of 30 to 45 and without diabetes were randomized to one of seven treatment arms, placebo, 46 milligrams topiramate, 92 milligrams topiramate, 7.5 milligrams phentermine, 15 milligrams phentermine, mid dose phentermine/topiramate combination, or high dose phentermine/topiramate combination, for a total of 28 weeks.

In study OB-301, the least-squares mean percent weight loss was 8.5 percent with mid dose phentermine/topiramate treatment, and 9.2 percent with high dose phentermine/topiramate treatment. Treatment

with phentermine/topiramate resulted in an additional 3 percent weight loss compared to the individual components, and the differences between groups were statistically significant. Therefore, the guidance standard for weight loss drugs used in combination was met with study OB-301.

After establishing additional efficacy over its components, the next objective is to determine a weight loss advantage over placebo by satisfying at least one of the efficacy benchmarks after one year of treatment, as outlined in the guidance document.

These benchmarks are, the drug's effect is significantly greater than that of placebo, with a mean drug-associated weight loss exceeding mean placebo weight loss by at least 5 percent; or the proportion of individuals who lose at least 5 percent of their initial body weight is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference is significantly greater in individuals on drug than in those on placebo.

As a reminder, there were two year-long

phase 3 pivotal trials to determine the efficacy of the phentermine/topiramate combination. Study OB-302 randomized adults with a BMI of 35 and greater and limited weight-related comorbidities in a 2:1:2 fashion to placebo, low dose, or high dose phentermine/ topiramate.

Study OB-303 enrolled adults with a BMI of 27 to 45 with two or more comorbidities, including type 2 diabetes. Individuals were randomized in a 2:1:2 fashion to either placebo, mid dose, or high dose phentermine/topiramate.

Treatment with all doses of phentermine/ topiramate for one year achieved a statistically significant least-squares mean percent weight loss compared with placebo treatment. Only low dose phentermine/topiramate did not achieve a 5 percent difference in mean percent weight loss over placebo. However, the proportion of individuals treated with low dose as well as the higher doses of phentermine/ topiramate, that achieved at least 5 percent weight loss, was statistically greater -- at least 35 percent -- and double the proportion of individuals

treated with placebo. The weight loss results observed in study OB-302 and OB-303 satisfied the division's efficacy benchmarks for a weight loss product.

These graphs represent the mean treatment difference from placebo for the measured weight-related endpoints in studies OB-302 and 303. The blue color represents the high dose combination, the red, the low dose combination, and the pink, the mid dose combination. Ninety-five percent confidence intervals that do not cross zero represent a statistically significant difference from placebo.

As expected, phentermine/topiramate-associated weight loss tended to be accompanied by improvements in waist circumference, lipids, blood pressure, and hemoglobin A1c.

A tabular representation of study OB-302 data is presented here. In individuals with a BMI of 35 and higher and limited weight-related comorbidities, improvements were observed on low and high dose phentermine/topiramate treatment. Only high dose phentermine/topiramate treatment demonstrated

consistent nominal statistical significance over placebo after one year of treatment. However, this study was not powered to detect significant differences in secondary endpoints.

Similar to the study data on the previous slide, in obese individuals with two or more weight-related comorbidities, there was statistical improvement in measured biomarkers. However, the changes were modest, and the clinical significance in terms of hard cardiovascular outcomes in this population with this drug is unknown.

These box plots represent the degree of weight loss of 10 or greater percent weight loss, 5 to 10 percent, zero to 5 percent, or weight gain with high dose phentermine/topiramate treatment and placebo treatment, and the resultant change from baseline in systolic blood pressure in study OB-302.

This representation of the data suggests improvement in systolic blood pressure is commensurate with amount of weight loss, regardless of treatment. This pattern was also demonstrated for other measured endpoints associated with weight such as diastolic

blood pressure, HDL cholesterol, triglycerides, and hemoglobin A1c.

In conclusion, individuals treated with phentermine/topiramate achieved significantly greater weight loss compared to its components. Individuals treated with low, mid, and high dose phentermine/topiramate achieved significantly greater mean percent weight loss, and the proportion of individuals achieving 5 percent weight loss compared to placebo.

Phentermine/topiramate-associated weight loss was accompanied by improvements in waist circumference, blood pressure, lipids, and hemoglobin A1c.

The clinical significance of improvements associated with phentermine/topiramate use long-term is unknown pending the results of the phentermine/topiramate cardiovascular outcomes trial.

I will now turn to the safety data.

First, as background, the integrated summary of safety for phentermine/topiramate was composed of three pivotal phase 3 trials and two supportive phase 2 trials. The trials were divided into two cohorts

based on duration of six months and one year. The cohorts were not mutually exclusive; therefore, some individuals were included in both the six-month and one-year cohorts. Because review of the six-month and one-year data did not present distinctly different results, this presentation focuses on the one-year safety cohort for phentermine/topiramate.

The one-year cohort consists of all randomized individuals receiving at least one dose of study medication from studies OB-302, OB-303, and all individuals who entered study DM-230, the six-month extension period to study OB-202.

This slide provides a summary of the overall exposure within the one-year cohort, adjusted for dose holidays, to phentermine/topiramate. Roughly a thousand people have been exposed to high dose phentermine/topiramate for one year. 335 have been exposed to mid dose, and 137 have been exposed to low dose for one year. Within the greater-than-12-month exposure group, the majority were exposed for no more than 58 weeks.

The first safety concern for discussion is

psychiatric adverse events. Briefly, there are case reports in the literature of psychosis associated with phentermine at doses of 30 to 180 milligrams a day. The majority of the cases were associated with a higher-than-recommended dose; however, there is one case report, from 1977, of a 20-year-old woman without a psychiatric history, taking 30 milligrams per day of phentermine, one month prior to a diagnosis of acute schizophrenic reaction characterized by paranoid delusions. Symptoms resolved with discontinuation of phentermine and treatment with Stelazine.

Topiramate has also been associated with psychiatric adverse events in patients with epilepsy. Mulla (ph) and colleagues reported 24 percent of 431 patients with epilepsy reported an adverse psychiatric event after topiramate initiation. Affective disorders were the most frequent. A family or personal history of psychiatric disorders, or a history of febrile seizures, were associated with these events. Others have published that a previous history of depression and rapid titration of topiramate increases the risk of developing depression.

It is important, when considering the psychiatric events that occurred in the phentermine/ topiramate development program, to consider the following relevant exclusion criteria.

Persons were excluded from participation if they had any history of bipolar or psychosis; more than one lifetime episode of major depression; a current history of moderate or higher severity depression, as determined by a PHQ-9 score of 10 or greater; the presence or history of suicidal behavior or ideation, with some intent to act on it; or antidepressant use that had not been stable for at least three months.

A total of 6700 people were screened for studies comprising the one-year safety cohort, and 4 percent failed due to the depression criteria. However, as mentioned earlier, almost 21 percent of individuals with a history of depression, defined as either history of depression or unstable treatment with antidepressants at baseline, were included in the one-year safety cohort.

The percentages were generally similar

between treatment groups, but high dose phentermine/ topiramate group had a slightly lower proportion of individuals with a depression history or on antidepressants.

To assess and monitor the risk of depression, the PHQ-9 questionnaire was administered at each study visit. The PHQ-9 is a depression scale composed of nine items based on the nine criteria on which the diagnosis of depressive disorders is based in DSM-IV.

This is a sample of the PHQ-9 questionnaire. Major depression is diagnosed if five or more of the nine depressive symptoms have been present at least more than half the days in the past two weeks. And one of the symptoms is depressed mood or anhedonia. A positive response to question 9, thoughts that you would be better off dead or of hurting yourself in some way, counts as present at all.

As a depression severity measure, the PHQ-9 score ranges from 0 to 27. A PHQ-9 score of 10 or greater is recommended as a screening cut point for major depression. Seventy-four percent of individuals

at baseline had no depression recorded by PHQ-9 score. There were no apparent numerical imbalances across all four treatment groups in terms of elevated PHQ-9 scores of 10 or greater, a worsening PHQ-9 score, defined as an increase of 2 or more severity categories, or in the frequency of a positive response to question 9, indicating possible major depression.

This table represents the mean PHQ-9 scores of individuals who experienced a depression-related event. The table is divided into those who discontinued versus those that did not discontinue due to a depression-related adverse event. Those that discontinued had a slightly higher average PHQ-9 score, but were still within the same category of severity. And there were also instances of discontinuation due to depression that had a corresponding PHQ-9 score of zero.

The presence of psychiatric disorders were also assessed by adverse event reporting using major preferred terms to code for one of these four subclasses, sleep disorders, anxiety, depression, and suicide/self-injury.

For orientation, this table represents the number and proportion of individuals experiencing the listed events on the left by treatment group. As a class, psychiatric adverse events occurred more frequently in phentermine/topiramate-exposed versus placebo-exposed individuals. Twenty-one percent of high dose-treated versus 10 percent of placebo-treated individuals experienced a psychiatric adverse event.

A greater proportion of individuals treated with phentermine/topiramate reported an event in the subclasses of sleep disorders, anxiety, and depression. These events were responsible for 26 percent of the discontinuations due to adverse events among phentermine/topiramate-treated individuals versus 12 percent of placebo-treated individuals. However, the proportions of individuals starting psychiatric medications during the studies were similar, and none of these events were considered serious by the clinical investigators.

This figure represents a graphical representation of the relative risk for the psychiatric disorder class divided by the three

studies that comprise the safety cohort and pooled relative risk of the high dose phentermine/topiramate.

Low and mid dose-treated individuals were approximately one and a half times, and high dose-treated individuals were two times more likely to experience a psychiatric adverse event compared to a placebo-treated individual.

This slide represents the data from the anxiety subclass. Any group with a confidence interval entirely to the right of the vertical dashed line is considered to have a higher relative risk compared to placebo. Individuals treated with high dose phentermine/topiramate were three times more likely to experience an anxiety-related adverse event.

This slide represents the depression subclass. Similar to the anxiety subclass data, individuals treated with high dose phentermine/topiramate in the two phase 3 trials and pooled data were two times more likely to experience a depression-related adverse event relative to individuals treated with placebo.

This table represents individuals with and

without baseline history of depression and incidence of depression-related adverse events. Overall, individuals with a baseline history of depression experienced a higher incidence of depression adverse events. Individuals treated with the phentermine/topiramate combination were more likely to experience a psychiatric adverse event compared to individuals treated with placebo, regardless of baseline history of depression.

Before discussing phentermine/topiramate and suicidality, I will briefly give the committee some background regarding topiramate and this issue.

In an FDA analysis of 199 pooled placebo-controlled clinical trials of 11 different antiepileptic drugs, including topiramate, patients randomized to one of these drugs had a statistically significant increased odds of suicidal behavior or ideation relative to placebo. The overall adjusted odds ratio was 1.8.

In July 2008, a joint advisory committee was presented this analysis, and voted there was a significant risk of suicidality with antiepileptics.

The labels of all antiepileptics must contain this information, but the committee stopped short of advocating a box warning.

This figure depicts the estimated odds ratio and 95 percent confidence intervals for suicidal behavior or ideation by drug, and all antiepileptic drugs used in the analysis combined. Of the patients included in the meta-analysis, the majority, 27 percent, were taking topiramate. Of the 11,000 topiramate-exposed patients, 72 percent were prescribed topiramate for an indication other than an underlying epileptic or psychiatric condition. The largest treatment indication within the topiramate group was for obesity, at 38 percent. Topiramate reached nominal statistical significance with an odds ratio of 2.53.

Now, with regards to the phentermine/topiramate program, the Columbia Suicide Severity Rating Scale, a prospectively administered questionnaire which tracks suicidal adverse events in clinical trials, was prospectively used in the phase 3 studies with phentermine/topiramate. The CSSRS

assesses both suicidal behavior and ideation, and provides a summary measure of suicidality.

There were no suicidal attempts, suicidal behaviors, or instances of serious suicidal ideation recorded by CSSRS. There was a slightly higher incidence in the measure of suicidality between the high dose phentermine/topiramate-treated group and placebo, and this result was driven primarily by suicidal ideation.

Within the clinical development program for phentermine/topiramate, there were three episodes of adverse events coded as suicidal ideation, one in a placebo-treated individual, which occurred after 194 days of treatment, and two in phentermine/topiramate-treated individuals, which occurred earlier after initiation of treatment, one at low dose on day 47 and one at high dose on day 24. All individuals had a history of depression and were on antidepressants at the time of the event.

In conclusion, there is evidence of increased psychiatric events associated with phentermine and topiramate in previous clinical

experience at doses generally higher than phentermine/topiramate. The PHQ-9 and CSSRS scores showed no imbalances in depression and suicidality.

Events recorded by the CSSRS were rare, and the sample size was relatively small compared to the exposures observed with rimonabant, a weight loss drug with increased risk of suicidality, and in the topiramate group in the FDA meta-analysis. Significant signals were seen in sample sizes of approximately 12,000 patients. Higher incidence of adverse events associated with sleep disorders, anxiety, and depression occurred with phentermine/topiramate treatment compared to placebo.

The second safety issue concerns neurocognitive adverse events. Topiramate is associated with impaired concentration and attention, memory loss, slowed thinking, and language difficulties at high and low doses, including doses less than 100 milligrams per day. Cognitive deficits have been related to dose and rapid titration of topiramate.

The sponsor has also theorized that some of

the expected side effects of the two drugs alone may be mitigated by effects associated with the other component. In particular, the cognitive slowing observed with topiramate treatment may be lessened with co-administration of phentermine.

Based on this known side effect profile, cognitive disorders were highlighted as a targeted medical event. This grouping was divided into four subclasses: attention, language, memory impairment, and other cognitive disorders not otherwise specified. This table again represents the number and proportion of individuals experiencing the listed events on the left by treatment group.

Phentermine/topiramate-treated individuals were four times more likely to experience a cognitive disorder compared to placebo. The effects observed were dose-dependent. The mid and high dose phentermine/topiramate-treated groups had higher proportions of events compared to placebo in all the cognitive subclasses.

Adverse events comprised 10 percent of the adverse events leading to discontinuation with

phentermine/topiramate treatment versus 5 percent with placebo treatment. No events were categorized as serious by clinical investigators.

To assess the effect of the combination of phentermine and topiramate compared to its components and placebo on cognitive function, the Repeatability Battery for the Assessment of Neuropsychological Status, or RBANS, was performed at baseline, week 4, and week 28 or early termination.

The RBANS is a battery of neuropsychological tests that measure five cognitive domains, including immediate memory, visuospatial/constructional, language, attention, and delayed memory.

This figure plots the placebo-subtracted treatment differences at weeks 4 and 28 for the RBANS total score. Confidence intervals not crossing zero represent a statistically significant difference from placebo. The blue box represents topiramate monotherapy at 46 and 92 milligrams. The red box represents the combination at mid and high dose. And the purple lines represent phentermine monotherapy at 7.5 and 15 milligrams.

In the topiramate and phentermine/topiramate combination group, the total index score showed statistically significant impairment at week 4, and in the high dose phentermine/topiramate group at week 28 compared to placebo. In general, the effects of the phentermine/topiramate combination mirrored the effects observed with topiramate monotherapy.

The main domain driving the overall total index score was the attention domain. Attention was impaired at weeks 4 and 28 with both topiramate monotherapy and mid- and high-dose phentermine/ topiramate compared to placebo.

The language domain score shows statistically significant impairment at week 28 for both topiramate monotherapy and for phentermine/topiramate combination, both strengths, against placebo.

No effects were identified on the immediate memory and visuospatial/constructional indices with phentermine/topiramate treatment.

Delayed memory was statistically significantly different at week 4 in the high dose

phentermine/topiramate group compared to placebo.

The effect observed in RBANS testing on attention mirrors the adverse events reported in the cognitive disorder class, with the majority of the cognitive disorders related to impairments in attention.

In conclusion, topiramate's effect on cognition has been well-established in individuals with epilepsy and migraines at low and high doses. Phentermine/topiramate similarly demonstrated a dose-dependent adverse effect on cognition in overweight and obese adults.

Although there was not formal statistical analyses of the combination versus the components, the RBANS testing suggests that the effects of topiramate were not mitigated by phentermine co-administration, and reflected the adverse events reported within the one-year safety cohort.

The third issue for discussion is the cardiovascular safety of phentermine/topiramate. First I would like to briefly address phentermine in the Fen-Phen combination. Although phentermine was a

component of the fenfluramine/phentermine combination, which was linked to increased risk for cardiac valvulopathy, current evidence indicates that the valvulopathy was attributable to fenfluramine and its metabolite norfenfluramine, which is a potent agonist of the 5-HT2B receptor. Activation of the serotonergic receptor is believed to represent the mechanism responsible for the valvulopathy associated with Fen-Phen.

Phentermine is a weak serotonergic agent, but assays have shown that phentermine does not have significant activity at the 5-HT2B receptor. Mechanistic evidence, therefore, does not support a causative role for phentermine in drug-induced valvulopathy.

The presence of cardiac disorders was assessed by adverse event reporting and grouped into two subclasses, cardiac arrhythmias and ischemic heart disease. Individuals were two times more likely to experience an adverse event related to cardiac arrhythmia, but the majority of these arrhythmias related to palpitations and tachycardia.

To further examine this signal, the change in mean heart rate and categorical increases in heart rate were assessed. Mean heart rate increased in individuals treated with phentermine/topiramate, with the largest main increase observed in the high dose group at 1.6 beats per minute over placebo. And when categorical increases were used to describe the effect of treatment on heart rate, a higher proportion of individuals treated with phentermine/topiramate experienced increases in heart rate of greater than 5, greater than 10, greater than 15, and greater than 20 beats per minute compared to individuals treated with placebo.

The second subclass within the cardiac disorder group was cardiac ischemic events. Within this subclass, there were similar occurrences of adverse events across all treatment groups. There was only one death within the phentermine/topiramate clinical development program, an cardiorespiratory arrest in a placebo-treated individual.

There were seven placebo versus eight combination-treated individuals that experienced a

nonfatal cardiac serious adverse event. And there was an equal number of cardiac catheterizations in both groups. There were three cerebral ischemic events, two in placebo-treated individuals and one in a high-dose phentermine/topiramate-treated individual.

Palpitations and tachycardia were the most common cardiac arrhythmias reported, and were more frequent in phentermine/topiramate-treated individuals. The clinical significance of favorable changes in blood pressure, with elevations in heart rate and its effect on major cardiovascular events, is unknown in the overweight and obese population.

The ischemic events were too few in number, which may be due to the enrollment of mostly younger women, to draw any conclusion regarding phentermine and its effect on major cardiovascular events pending the results of the phentermine/topiramate cardiovascular outcomes trial.

The incidence of metabolic acidosis with phentermine/topiramate use is the fourth item for discussion. Topiramate's activity as a carbonic anhydrase inhibitor is associated with a

hyperchloremic metabolic acidosis. Chronic untreated metabolic acidosis may increase the risk for nephrolithiasis, osteomalacia, or osteoporosis, and affect growth in children. A marker of metabolic acidosis is a low serum bicarbonate concentration.

When evaluating the effect of phentermine/topiramate on mean change in bicarbonate levels, a small decrease is observed with phentermine/topiramate treatment. However, when examining the proportion of individuals reaching a bicarbonate level less than 21 or 17, one can discern a dose response relationship with phentermine/topiramate use.

Approximately 30 percent of high dose-treated individuals versus 6 percent in placebo-treated group had a bicarbonate of less than 21, and 13 percent of phentermine/topiramate treated versus 2 percent in the placebo-treated group had persistently low bicarbonate levels, defined as a low bicarbonate at two consecutive visits or at the final visit.

Although smaller in magnitude, a similar relationship was observed with markedly low bicarbonate levels of less than 17, with 2 percent in

the high dose-treated group versus .3 percent in the placebo group, at any time post-randomization.

I stated previously metabolic acidosis may increase the risks for nephrolithiasis, and an imbalance was observed with this adverse event with high dose treatment versus placebo treatment.

In conclusion, there were imbalances noted in frequency of bicarbonate less than 21 and 17 with phentermine/topiramate treatment compared to placebo treatment. A large proportion of high dose phentermine/topiramate-treated individuals, 30 percent, had a bicarbonate less than 21. A greater number also had a higher occurrence of nephrolithiasis compared to placebo-treated individuals. The long-term effects of phentermine/topiramate-associated metabolic acidosis on bone health and growth is unknown.

The final safety topic concerns the teratogenic potential with phentermine/topiramate use. Topiramate is a teratogen in several animal species. In mice, topiramate is teratogenic at two times the high dose of phentermine/topiramate, or essentially

equivalent to clinical exposure. The abnormalities noted are primarily craniofacial. Based on an area under the curve comparison, topiramate is associated with teratogenicity in rabbits and rats at 6 and 34 times high-dose phentermine/topiramate, respectively.

These studies represent a relatively wide range of sensitive, 2 to 34 times high dose phentermine/topiramate across species. However, teratogenicity occurs in all three species tested, and it is difficult to extrapolate where humans fall along this spectrum of sensitivity.

The sponsor completed embryo fetal studies using the phentermine/topiramate combination in rabbits and rats at one and two times the high dose clinical exposure. No teratogenic effects were noted. However, the maximum doses of topiramate used are not associated with teratogenesis in either species.

These studies were not designed to assess toxicity at teratogenic doses of topiramate. Rather, these studies were designed to investigate potential additive or synergistic effects of the combination on embryo fetal development at a non-teratogenic dose of

topiramate.

Therefore, although there were no significant drug interactions resulting in teratogenesis at the doses of phentermine/topiramate tested, this does not negate the known teratogenic profile of topiramate in multiple species.

Human pregnancies' exposures to antiepileptic drugs have been monitored by several pregnancy registries, some of which include the United Kingdom Epilepsy and Pregnancy Register. In 2008, this group published information regarding outcomes of pregnancy exposed to topiramate. Of 70 topiramate monotherapy-exposed pregnancies, there were three major malformations, for a calculated malformation rate of 4.8 percent. Two of the malformations were oral cleft abnormalities at 200 milligrams per day and 600 milligrams per day.

Unfortunately, duration of exposure and treatment indication were not detailed in the article. Furthermore, the lack of a control group associated with this registry means the relative risk cannot be calculated.

However, the North American Antiepileptic Drug Pregnancy Registry has established a control group to calculate relative risks with antiepileptic drug exposure in pregnancy. In an abstract presented at the Teratology Society meeting this June, the prevalence of major malformation was 3.8 percent for topiramate monotherapy-exposed pregnancies. The relative risk of major malformation with topiramate exposure was 2.8, with a 95 percent confidence interval of 1 to 8.1 when compared to controls.

Four infants exposed had cleft lip, two of which were isolated. And the expected prevalence of isolated cleft lip is .07 percent, or a crude odds ratio of 10. There was also an increased risk for low birth weight in infants exposed to topiramate in utero compared to controls.

The authors concluded that topiramate monotherapy was associated with a higher risk of major malformation and low birth weight compared to controls. The doses of topiramate were not included in the abstract, but it could be assumed that the majority of the doses were higher than what is seen

with phentermine and topiramate.

Additionally, the FDA adverse event reporting system was queried for adverse event reports of topiramate-exposed pregnancies, which resulted in 64 unique cases which specified a malformation and was not confounded by an underlying genetic condition. There were more cases of topiramate exposure that were pulled from the registry; however, these were the 64 that were analyzed.

Of these cases, the majority of the malformations were craniofacial, with cleft lip and/or palate predominating, and several of these also had concurrent malformations, so it was not an isolated event. Of these cases, 88 percent were exposed in the first trimester. Fifty percent did not continue treatment past the first trimester, and the adverse events reported at doses of 200 milligrams and lower were not different compared to higher doses, although the number of pregnancies exposed to doses over 400 milligrams were small.

The teratogenic potential of topiramate may be dose-dependent, given that doses used to treat

epilepsy are higher than the maximum dose of phentermine/topiramate. However, when the clinical exposure data from patients with epilepsy on Topamax and other medications were compared to separate pharmacokinetic data from the phentermine/topiramate development program of obese individuals, the maximum concentration from the 100 milligram formulation of phentermine/topiramate overlaps the exposure observed with the indicated treatment dose for epilepsy of 200 milligrams Topamax twice a day. Therefore, we cannot be completely reassured by the lower dose of topiramate in the phentermine/topiramate combination.

Turning to the phentermine/topiramate clinical development program, women of childbearing potential were allowed to participate provided they agreed to use double barrier or oral contraceptive therapy plus single barrier contraception and had a monthly negative urine pregnancy test.

Despite these precautions, 34 pregnancies occurred during the phentermine/topiramate clinical development program. Nineteen pregnancies delivered. There were an equal number of elective and spontaneous

terminations that occurred.

The majority of pregnancies occurred in the high dose group, and 13 of the pregnancies occurred when oral contraceptive therapy and single barrier method was the method of contraception reported. All women discontinued study drug upon notification of pregnancy. The average gestational age was 5.4 weeks at diagnosis, and no anomalies were noted on newborn physical exam.

Other issues to consider regard phentermine/topiramate's interaction with oral contraceptive therapy. Co-administration of multiple one-state doses of high dose phentermine/topiramate with a single oral contraceptive dose containing 35 micrograms ethinyl estradiol and 1 milligram of norethindrone decreased the ethinyl estradiol concentration by 16 percent, and increased the norethindrone concentration by 16 percent. It is unclear how much a decrease in hormone concentration will allow pregnancy to occur. However, the increase in norethindrone may be in favor of maintaining the contraceptive efficacy.

Other considerations for women and obesity and the issue of pregnancy planning and prevention include the higher rates of contraception, non-use in obese women and adolescents, the increased risk of venous thromboembolic disease with obesity, and the potential for higher risk of embolic disease with oral contraceptive use, and that a woman's fertility may be increased with weight loss. And this fact may partly explain why the majority of pregnancies occurred in the high dose phentermine/topiramate-treated group.

In conclusion, it is a concern that there appears to be a repeated pattern of craniofacial congenital malformation observed in animal studies, separate pregnancy registries in the United Kingdom and North America, and within the FDA AERS database.

We acknowledge that there are limitations within these databases. However, the incidence of 34 pregnancies in a controlled clinical program underscores the high likelihood of phentermine/topiramate exposed pregnancies, and the necessity to discuss these data and inform women and their health care providers of the benefits and risks

with phentermine/topiramate use.

This slide summarizes the benefit/risk profile of phentermine/topiramate for the weight management indication. The potential benefits for some individuals include significant weight loss. Almost 70 percent of overweight and obese individuals treated with high dose phentermine/topiramate lost 5 percent of their body weight, compared to 20 percent in the placebo group. And almost half of overweight and obese adults treated with high-dose phentermine lost 10 percent of their body weight, compared to 7 percent in the placebo group. In addition, an improvement was observed in weight-related comorbidities.

The potential risks for some individuals with phentermine/topiramate use include a 1 and a half to 2 times higher risk of psychiatric adverse events; a 4 times higher risk of cognitive impairment; an increased heart rate, with 20 percent of high dose-treated individuals with a heart rate increase of 20 beats per minute over baseline compared to 12 percent in the placebo group.

Metabolic acidosis was more common in the phentermine/topiramate adults. Thirty percent versus 6 percent had a bicarbonate level of less than 21 milliequivalents per liter in the high dose phentermine/topiramate and placebo groups respectively. Lastly is the concern for possible teratogenicity, particularly craniofacial abnormalities with phentermine/topiramate use.

I'd like to acknowledge all the members of the review team for their hard work and support in the review of the phentermine/topiramate drug application.

Finally, we have prepared the following questions for your discussion and input.

Number 1. Taking into account the results of the assessments made with the PHQ-9 and the Columbia Suicidality Severity Rating Scale, please comment on the significance of the increased adverse event reports of depression, anxiety, and sleep disorders in subjects treated with phentermine/topiramate. If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

Number 2. Please comment on the potential significance of the increased adverse event reports of disorders of attention, memory, language, and other cognitive disorders in subjects treated with phentermine/topiramate. If approved, please discuss need for monitoring and possible monitoring strategies.

Question 3. Please comment on the potential clinical significance of the metabolic acidosis determined by decreases in serum bicarbonate levels with phentermine/topiramate treatment. If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

Number 4. Please comment on the potential clinical significance of the increase in heart rate observed in the phentermine/topiramate-treated individuals. If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

Number 5. Given the doses of topiramate in phentermine/topiramate, please comment on whether you believe phentermine/topiramate poses a teratogenic

risk to the target population for weight loss. If you believe it does pose a risk, please comment on how this risk should be managed in women of childbearing potential if phentermine/topiramate is approved.

Lastly, based on the current available data, do you believe the overall benefit/risk assessment of phentermine/topiramate, or Qnexa, is favorable to support its approval for the treatment of obesity in individuals with a BMI of 30 or greater, or 27 and greater with weight-related comorbidities?

If voting yes, please discuss the basis for this recommendation, any labeling recommendations, and discuss whether additional studies should be conducted post-approval.

If voting no, please discuss the basis for this recommendation. Please discuss what additional studies would be necessary to address any outstanding deficiencies. Thank you.

DR. BURMAN: Thank you very much.

The floor is now open for questions to the FDA from the committee.

Dr. Weide?

DR. WEIDE: Yes. My question is related to the teratogenicity. In slide 71, you said that the major malformation rate was 3.8 percent, which is close to what we saw with the Motherisk data that was presented. But the sentence under that says that there's a relative risk of 2.8 compared to controls, whereas in Motherisk it looked like it was equivalent to controls.

Can you comment on why there's a difference and what that means?

DR. ROBERTS: This is from the abstract that should be in your folder that was presented at the Teratology Society meeting. And in that registry, there are two control groups that they've used. One is an internal control group, which is made up of people that are known to the women that are enrolled. So they ask women who are enrolled in the pregnancy registry to also recruit their friends or family members. So they tend to have like a demographically matched control group. Then there's an external control group, which is comprised from the Brigham and Women's Hospital. And it's roughly about 200,000

women that they've looked at the congenital malformations of.

So this relative risk was using the internal control group, which is a group matched for demographics, age, and it's recruited by the women that are enrolled in the pregnancy registry.

DR. BURMAN: Thank you.

Dr. Rogawski?

DR. ROGAWSKI: I wonder if you could clarify your interpretation of the suicidality information. It sounded to me like the sponsor was concluding that there was not any increase in suicidality measures. And your assessment, I sense, is different.

Can you compare those two?

DR. ROBERTS: I think that the CSSRS doesn't show any signal. That was done, though, in a much smaller sample size than the sample sizes that saw a positive signal for suicidality. From rimonabant, there was about 13,000 patients there, and in the topiramate group that I referred to in the FDA meta-analysis, there was 11,000.

So it may be although there was not a signal

seen within this sample size, it is smaller than perhaps the sample size needed to see a positive safety signal. And that's the only thing I'm pointing out.

DR. ROGAWSKI: And if I could follow up on that, you alluded to the fact that the FDA antiepileptic drug and suicidality analysis included patients taking topiramate for indications other than epilepsy. I wonder if it was possible to break that down into patients who were indeed taking it for epilepsy versus for weight loss or migraine headache and so forth.

DR. ROBERTS: Yes. Thirty-eight percent in that group were in an obesity trial. So they were the largest proportion of the topiramate group.

DR. ROGAWSKI: But did they break down the suicidality measures by the use of the drug?

DR. ROBERTS: They did. And I do think we have that information. I don't know if it's been made public or not. But I think that information, we do have.

DR. ROGAWSKI: That would certainly be

useful.

DR. BURMAN: So we're not going to hear any more about that?

DR. ROBERTS: I'll have to confer with the neurology division.

DR. BURMAN: Sure. Sure, whatever.

Dr. Morrato?

DR. MORRATO: Yes, thank you.

In the briefing materials, it said that the maternal health team recommended for Qnexa a pregnancy category classification of X, which, just to read the definition, is, "Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from the drug, or marketing, or both; and that the use of the drug in a pregnant woman clearly outweighs any possible benefit, that is, there are safer drugs or other alternatives that are available."

So as we will be discussing later how to manage risk and so forth, I don't know if you're able to share with us whether or not the agency -- how they view category X in terms of REMS strategies. That is,

do you make a distinction in the type of program that might be applied in different drug situations, or is there really a movement within the FDA to try and come up with a common goal and common approach for category X drugs in terms of managing the risks?

DR. ROBERTS: That's a good question. I know there's representatives of the maternal health team that might be able to help us with that question.

Dr. Best?

DR. BEST: Yes. I'm Jeanine Best from the pediatric and maternal health staff. I'm a reviewer on both the pediatric and maternal health teams.

There is no consistent program for pregnancy X drugs because when we look at pregnancy category X drugs, we're looking at the potential benefit for use in a pregnant woman. And one of the reasons why we recommend a pregnancy category X for a weight loss drug is because there's no benefit for using the drug in a pregnant woman because there is an obligatory weight gain in pregnant women just due to the weight gain needed in the maternal tissues.

I think the other consideration here --

we're just talking about topiramate; we also need to consider phentermine and the possible adverse effects of phentermine on a pregnancy. Phentermine is a stimulant which has vasoconstrictive activities, and there's a potential decrease in uterine blood flow. And that has not been brought up. But we also need to consider the adverse effects of phentermine on a pregnancy.

But when we look at pregnancy category X drugs, we consider the indication for use. And if you look at oral contraceptives, all oral contraceptives are pregnancy category X because there is no indication for contraception in a pregnant woman.

DR. MORRATO: Just a real quick follow-up, then.

Did you have discussions in how you look at the indication of weight loss versus the indication of treatment of severe acne? In terms of -- if you're making that -- we're going to have to make a distinction on how we manage the risk, and that's a balance of -- if I'm hearing you correctly, the level of program is dependent upon what the indication is

and so forth.

DR. BEST: It's dependent on the indication, and it's also dependent on the signal that's been seen.

DR. BURMAN: Thank you.

Dr. Hendricks?

DR. HENDRICKS: I'm referring to slide 57, categorical changes in heart rate. And I'm wondering if any effort was made to look at the JCN-7 categories because I suspect that if you looked at the last line there, the patients that have greater than 20 increase in heart rate, most of those would probably be hypertensive patients.

DR. ROBERTS: No. We did not further classify it. So the sponsor may have done that analysis.

DR. HENDRICKS: Because from a clinical standpoint, I think it's more important to look at the JCN-7 than simple increases in heart rate or blood pressure.

So that wasn't looked at?

DR. ROBERTS: No. But it looks like the

sponsor may -- we can defer to the sponsor and see if they've done that analysis. But no, we have not looked at it.

DR. HENDRICKS: Thank you.

DR. BURMAN: Has the sponsor done that analysis? Please.

DR. GESUNDHEIT: Thank you. We haven't done that analysis. But I wanted to clarify because it wasn't crystal clear that when you look at these heart rate outliers, it's on one occasion that they had that degree of heart rate increase. It almost came across as if it could have been a mean.

But we measured heart rate about 15 times over the course of one year. If on any one occasion -- I think that's the analysis here -- they had an increase more than baseline of that degree, then they would register on this analysis here.

DR. BURMAN: Thank you.

Dr. Heckbert?

DR. HECKBERT: Yes. I have a question about the teratogenicity findings again. So you mentioned that in the Hernandez Diaz paper, where we have the

abstract here, they used this control group or the comparison group of friends and family members referred by the subjects, by the women taking the antiepileptic drugs.

So the prevalence of major malformations in that comparison group was 1.3 percent. And then you mentioned -- I don't think it's in the abstract -- is it Brigham and Women's Hospital control group? I don't think it's in the abstract.

What's the expected rate of major malformations in that group?

DR. ROBERTS: It's 1.6.

DR. HECKBERT: Okay. And that is supposed to be a general population of women.

Can you tell us any more about that group?

DR. ROBERTS: It was started by Dr. Holmes. I believe he started it back in the late 1970s. And it looks at women and their babies that delivered at Brigham and Women's Hospital. I think it has a sample size of around 200,000.

DR. HECKBERT: I was just wondering how that compares with -- I guess the figure that the sponsor

gave of 3 point something percent expected is because those were women with epilepsy. I don't know if the sponsor wants to comment on that.

DR. BURMAN: Please.

Dr. Cragan, did you want to respond?

DR. CRAGAN: Yes. I actually sit on the advisory committee of the North American AED Registry, and they employ a very restricted case definition to the malformations that excludes all known genetic conditions, all chromosomal abnormalities, and really look at malformations that are unexplained by any other factors.

I think one has to be careful in comparing prevalences of malformations across studies that perhaps use different case definitions or different methodologies. So I think the internal comparisons within that is partly why the control malformation rate is so low, but is an advantage of that registry.

DR. BURMAN: And did the sponsor have a quick response as well?

DR. KOREN: Thank you. Concurring with some of the committee members' comments, any collection

that comes to one-half percent malformation rate in the general population is not where it is. It's typically 3 to 5 percent. And some of the databases used in the North American ones have very low.

These are the comments that happen in the Teratology Society, and they are very different from many other databases. So if the exposed group have 3 to 3 and a half percent -- and do remember, the control group -- the exposed groups, as seen by Lou Aronne is a team of teratologists that check them microscopically; whereas the control group come from many thousands of women not checked by Lou Aronne and his team, the big one; the internal one is.

So I just want to draw attention to the fact, as one member of the committee said, it's very much depend upon how you choose your control groups. And I think Dr. Roberts also said so. You should remember there were other databases that didn't come to the same conclusions. Out of four or five, not all of them find this, either.

DR. BURMAN: Thank you.

Dr. Bersot?

DR. BERSOT: Back to the issue of metabolic acidosis. You mentioned that in the high-dose treatment groups, about 30 percent of them had bicarbs less than 21, since topiramate's responsible for that and it's renally cleared.

Was there any relationship between estimated GFR or creatinine levels and bicarb values?

DR. ROBERTS: I didn't look specifically at creatinine clearance. And I did ask the sponsor to look at like doubling of the creatinine, and I can't remember off the top of my head that number. We did not do a specific analysis looking at the level of bicarbonate and GFR or creatinine clearance, but something to consider.

DR. BERSOT: Thank you.

DR. BURMAN: Did you have a follow-up on that? No?

Dr. Flegal?

DR. FLEGAL: Yes. I had a couple of questions, maybe a little bit somehow off target, but in terms of safety.

One is the issue of weight regain after

stopping, after cessation of the drug, and what the characteristics of that weight regain itself might be like, is there some expected difference of some kind between other kinds of weight gain.

Another sort of related issue is the possibility that a woman would use this product to lose weight before becoming pregnant, and then have both weight regain after cessation of the drug plus pregnancy-related weight gain, and whether that was felt to be additive or exactly what the effect of that would be.

Another issue is, has FDA considered all the probability of use in women who are below these weight categories? Because by my calculations, about 80 percent, literally, of young white women with a BMI of 23, 80 percent would like to weigh less. And so it seems like for this particular kind of drug, there's a very large probability of use in people for whom it's not recommended.

Has there been any thought to evaluating that in some way?

DR. ROBERTS: I think those are all issues

that we have discussed internally. Except for the first one, I can't really speak to the quality of the weight regain. I do not know that answer.

We have talked about the occurrence of women who would like to lower their pre-pregnancy BMI for many good reasons that might be on this drug, and how to incorporate that into good pregnancy planning and prevention if the drug was approved. And I think that there are many challenges to that, and we hope that the panel will help us with that.

Then, I'm sorry, there's a third question.

DR. FLEGAL: Well, just the high interest in weight loss in women who don't have the indications for the drug, like the high interest or the desire to lose weight in women who are lower weight, And has that been considered, how to assess that or how to assess the probability in some way that this drug will be used by women with BMIs of 22 and 23? Because 80 percent of them would like to weigh less.

DR. ROBERTS: Of course, yes. I think that's a real important question and issue as well. I think that you could look at compliance prescription

data. I don't know how insurance companies reimburse for obesity drugs, if you have to put your BMI on a prescription slip, and I don't know how valid that would be or not.

But that's just one idea that I've come up with. But I would sure be interested in any discussion on how to monitor that because I do think that that is an issue.

DR. BURMAN: Thank you.

Dr. Bersot, you had a quick follow-up?

DR. BERSOT: Not quite on these topics, but related to the issue of BMI as qualifying for treatment initiation. The cut points are 30 and 27 that you've included here. It's well-known that there's increased risk of insulin resistance in diabetes in Southeast Asian people with BMIs considerably lower than this.

Is there some reason why the cut points of 23 and 27 wouldn't be used for people specifically from the Indian subcontinent and Filipino individuals? Because there are very high incidences of diabetes and insulin resistance in those groups, and at BMIs much

lower than these that you have listed in what appears to be the coming indication.

DR. ROBERTS: Right. We haven't discussed with the sponsor any additional indication for that particular group. And off the top of my head, I can't think of the actual proportion of people that were included in these trials, but it was a very, small, small number.

DR. BERSOT: But looking at BMI --

DR. ROBERTS: Probably, yes. Yes. So it would be hard to say what it would look like without getting further studies in that particular group.

DR. BURMAN: Thank you.

Dr. Kaul?

DR. KAUL: Yes. Thank you. The real world environment for the use of this drug is going to be a lot more permissive than these trials with regards to cardiovascular risk. And so my questions relate to did you identify any subset of population where the increase in heart rate could potentially have clinical relevance?

Going back to slide 57, which you already

have it, I would have liked to see this data presented according to the baseline stratum of heart rate. If the heart rate of greater than 20 beats per minute is clustered in the lower end of it, then it's less concerning.

But if somebody has a baseline heart rate of 90, and you've just shown us a category of greater than 20 but we don't know what the upper ceiling for that is, and if it happens only in patients with a history of MI, where there were only about 44 patients in the entire program with a history of MI, you can see how this could be clinically relevant.

DR. ROBERTS: Yes. And I believe, in the sponsor's briefing document, they talk about baseline heart rate and then looking at these increases. And if I am remembering correctly --

DR. VELTRI: Table 26.

DR. ROBERTS: -- it's people on the lower end of the heart rate stratum that have the most increase in heart rate throughout the study. Please correct me if I'm wrong.

DR. BURMAN: Dr. Veltri?

DR. VELTRI: Yes. It's in table 26 of the briefing document. And Dr. Kaul is exactly right. The changes are predominately in those less than 60 beats per minute of baseline. If you look at those between 60 and 90, they're pretty flat, and actually, they tend to go down across all treatment groups in those greater than 90. So that is reassuring.

DR. BURMAN: Does the sponsor have a quick response?

DR. GESUNDHEIT: Yes. Could I show that table?

If we could show the table looking at heart rate changes.

But what we looked here was the change in heart rate as a function of the baseline heart rate. And so what you see at baseline is we had patients who at baseline had bradycardia, patients with heart rates between 60 and 90, and then patients with heart rates that were greater than 90 at baseline.

What you see then shown is the change in heart rate at week 56, when they actually exited the study. And so what you see is the patients with the

slow heart rate actually had the greatest increase in heart rate at study exit. Those that had normal heart rates in the normal range were really pretty much the same, with just a slight increase, in the top Qnexa group. And the patients who started out with a high heart rate at baseline actually showed a mean decline in heart rate at all the three Qnexa doses at study exit.

So I agree with the comment that that would tend to mitigate the concern about the heart rate effect because some of the increase in heart rate is actually happening in patients who at baseline actually had bradycardia.

DR. KAUL: I'm also interested in excluding the possibility whether there were certain patients that were identified that had an elevated blood pressure response rather than reduced blood pressure response. So perhaps one way to look at is did you collect the blood pressure information in OB-201 study, where you looked at the individual components versus the combination? Because I would have expected that phentermine would increase the blood pressure.

DR. GESUNDHEIT: Yes. Yes, we can show those data because actually we were looking for mitigation of some of these cognitive and other effects that we really didn't see, as Dr. Roberts outlined.

But we did see mitigation on the heart rate and the blood pressure effect. So first, if you look at heart rate, this is the study where we had the separate components as well as the combination. And so here you see the effect from baseline to exit on heart rate in the placebo patients. This is now the phentermine at the two doses, and it shows, as you might expect, a slight increase in heart rate.

But what you see with the topiramate is it does cause a decrease. And when you combine the two -- - this is then the combination of the low dose of phentermine and -- mid dose, rather, of phentermine and topiramate; this is the high dose phentermine and topiramate -- you see that there overall is very little change, so that the topiramate is able to blunt the increase in heart rate that could be induced by the phentermine.

DR. KAUL: What about the blood pressure?

DR. GESUNDHEIT: Yes. Let me just show the blood pressure as well.

This was the effect on systolic blood pressure. And what you see is that with placebo, there was very little change. I think some of this lowering could just be a white coat effect, so there was a slight lowering even in the placebo patients, or it could have been related to their weight loss that their systolic blood pressure went down a little bit.

The phentermine alone actually caused a very slight reduction in blood pressure. The topiramate caused a greater reduction in blood pressure. I think more illustrative is the Qnexa top dose, when it looks, if you will, like a blend between the effect of the phentermine and the effects of the -- I'm sorry. If you look at the effects of the phentermine here and the effects of the component of topiramate, that more or less equals what you see with the combined drug. Overall there was a lowering of the systolic blood pressure with the combination.

DR. KAUL: Were there any patients where you

saw the opposite effect?

DR. GESUNDHEIT: We looked, for instance, at the patients who had an increase in heart rate and an increase in blood pressure. That was the outlier analysis that I showed earlier. And there were very few patients who really showed that combination of both an increase in heart rate and an increase in blood pressure.

As I showed earlier, for those patients who had an increase in heart rate, almost all of them had actually a decline in their blood pressure so that their rate-pressure product changed only slightly.

DR. BURMAN: Thank you.

We have 15 minutes for probably seven or eight questions. Please be succinct.

Dr. Goldfine?

DR. GOLDFINE: So before you sit down, one of my questions -- because I had also noticed that it was the patients who was more bradycardic who had the increase in heart rate. And on slide 33, you had actually showed that a number of them actually had decreases in their blood pressure meds. And I'm

wondering if there's any confounding by beta blocker dose reduction.

DR. GESUNDHEIT: We actually had very few patients using beta blockers. But yes, this slide just shows the effect you mentioned. In general, as Dr. Day reviewed, when we looked at the blood pressure effects and we allowed patients to have their blood pressure medicines adjusted as if they were being taken care of in regular clinical practice, we actually saw a decrease in the use of blood pressure antihypertensives in the patients on Qnexa, both at the mid and the top dose, with some addition of antihypertensives in the placebo patients.

But we can break that out if you'd like to actually look at the beta blocker effect. I think we may be able to look at that, if you would like us to examine that more carefully.

DR. GOLDFINE: I actually just wanted to know for the beta blocker effect on heart rate.

Then I had one other question, and I'm not sure which of the two of you is better. But it's on the non-responder rate. And there was some discussion

in the background material we were provided, but not anything really presented, about that if people did not lose weight early, that that seemed to predict their response throughout the trial.

What I really want to try to tease that out a little bit is to stop people from continuous exposure, especially women who might get pregnant if they're not also having the benefit of the drug. And I'm not sure which of you would be better to ask a non-responder question to.

DR. GESUNDHEIT: Let me ask Dr. Day to answer that question.

DR. DAY: We did assess non-responders. We define non-responders as those that had less than 5 percent overall weight loss at the end of the study. We examined kind of predictive measures to find non-responders early, looked at demographic disease variables and really didn't find anything predictive in that.

What we ultimately did is we looked at a cumulative distribution, and we looked at kind of the prediction by quintile of weight loss in this analysis

that would suggest low weight gain -- I mean, low weight loss at the end of study.

What we saw, to try to make it brief, is we saw a very consistent effect at three months of weight loss that predicted a low effect of weight loss at end of study. So what this suggests is that subjects that lose like less than 3 percent within two to three months are the most likely subjects to have the lowest weight loss effect overall at end of study.

So I think what that tells us is if they don't lose weight early on, with a fairly high degree of certainty, 85 to 90 percent degree of certainty, we can predict that those subjects will have a lower degree of weight loss at end of study.

DR. BURMAN: Thank you. I'd like to refocus a little bit on the FDA analysis, although later we'll have time for both.

Dr. Proschan, did you have a question?

DR. PROSCHAN: Yes. One thing I wanted to point out is part of what you're seeing when you look at the people who started out with high heart rate, and then you see that they went down, is just

regression to the mean. You would see that even if you gave no drug; if you measured someone and they ended up high, in high level, at baseline, they're going to go down.

But the question I had got back to the North American registry. You mentioned that there were two control groups. And I'm wondering, did they give the numbers for the internal control group, the friends and family, the numbers of those women who had malformations and how many of those women there were?

DR. ROBERTS: They don't particularly in the abstract. They do not break down the types of malformation within that control group. It's roughly about the same size, so it's still like around 350 or so women. But I don't know, within that group, what type of malformations are noted.

DR. BURMAN: Thank you.

Dr. Thomas?

DR. THOMAS: Two questions. First one is about the issue with using last observation carried forward or completion. One of my former professors, Jim Ware, wrote an article, an editorial in the New

England Journal of Medicine, about 2003 or 2004. And as we know, weight loss studies are plagued by this fact that there are very low rates of completion, a lot of dropouts.

When you use these two methodologies, you tend to over-inflate the differences. He suggested, actually, to use a very conservative method, which is you use the baseline value forward in the study because the baseline value is actually going to bias you towards a null result.

Has that analysis been done, and would that affect actually what the findings are?

DR. ROBERTS: The FDA has not done a baseline carried-forward observation. We did the analysis according to our guidance, which does not have that as part of that, but the sponsor may.

DR. BURMAN: Does the FDA have that analysis, quickly? I'm sorry, sponsor? Thank you.

DR. ALLISON: Thank you. My name is David Allison. I'm a professor of biostatistics at the University of Alabama at Birmingham and an obesity researcher. I'm a paid consultant to Vivus, and I'm

representing only my own opinion, not my university's.

So in response to the question, it is of course a concern always when there are dropouts in studies. We wish we didn't have dropouts. But it is true of virtually every obesity clinical trial ever done.

In order to address that, we used virtually all of the major methods that have been promoted to analyze data with dropout and intent to treat. We did completers only intent to treat with a mixed model, intent to treat with -- yes, can we get the slide up?

What you see here is a number of different studies we've done. So we've done multiple imputation, multiple imputation two different ways. We've done a mixed model, completers on drugs with no imputation. And no matter how we analyze the data, the conclusions of statistical significance remain the same. The estimates vary a little bit, but not hugely.

We also did the baseline observation carried forward that the panelist has referred to.

Can we get that one, that slide? Okay.

We don't have a slide of that, but we've done those analyses. And in each case they remain statistically significant, albeit the estimates are altered. But the statistical significance of the group differences remains the same.

DR. BURMAN: Thank you.

DR. THOMAS: Just very quick. The second question is in the number of cases overall between placebo and Qnexa, there's four cardiac cases that ended up having cath and there's four that had MI and there are four that had MI and Qnexa.

Phentermine has a contraindication to be used in atherosclerosis or risk of atherosclerosis, yet there's a plan for a cardiovascular outcome trial. To actually complete that, you're going to have to use people at high risk for an event.

So are you suggesting that topiramate has some beneficial effect that abrogates the effect of phentermine on atherosclerotic disease, or are you suggesting that phentermine doesn't have this contraindication to be used in people with atherosclerotic disease?

DR. BURMAN: I assume you're asking the sponsor?

DR. THOMAS: No, the FDA.

DR. BURMAN: The FDA? Okay.

DR. ROBERTS: With regards to phentermine, which was approved back in 1959, I think because of its elevation in heart rate and its elevation in blood pressure, that's why that contraindication was put in there for advanced arteriosclerosis and cardiovascular disease.

In regards to the Qnexa with the phentermine as part of that drug combination, I think it is important to find out what the pharmacotherapy benefits are with weight loss in regards to major cardiovascular events. And frankly, I don't know if we would get that type of study done with phentermine.

So I think this question needs to be answered. And if this drug is licensed, I think that's an important question to answer, frankly. I don't know if we would have it with phentermine alone. And because of its elevation in blood pressure, I think that's why those contraindications were there.

And certainly, with this drug product, blood pressure does not seem to be as much of a concern.

DR. BURMAN: Thank you. We have about five minutes, so we're not going to get to all of the questions. I think Dr. Henderson is next.

DR. HENDERSON: Yes. The sponsor states that the cognitive side effects are reversible. Could you comment on that?

DR. ROBERTS: I can only point to the RBANS testing, which -- I don't know if I can find it -- which looked at this at week 4 and at week 28. And you can see, for the total score -- sorry -- that there was a more significant decrease in total cognitive results.

So this is for the total score. And you can see that at week four, that's the topiramate monotherapy, and it's statistically significant from placebo. And it's also seen in phentermine at week 4. But the effect is somewhat lessened at week 28. So in the high dose, it doesn't completely go away; it's still there, based on this testing.

You can still see that for the attention as

well, that it does still remain at week 28. I think the sponsor talked about the duration of some of the cognitive events, and that the onset was within the first few months. So I can only speak to this, that it appears that there is some lingering effect, in particular with attention, and then the adverse event reports.

From what I've looked at, it looks like they certainly resolve with discontinuation of the drug.

DR. BURMAN: Thank you.

Dr. Rogawski?

DR. ROGAWSKI: The sponsor mentioned that women made up the predominate group of both pivotal the 302 and the 303 trials. Eighty-three percent of the subjects in the 302 trial were female, and 70 percent in the 303 trial.

I'm wondering if the agency or the sponsor has broken down the analysis to look at the effects in either sex. And really, that gets to the question of whether we know is this drug efficacious in males, or is it only efficacious in females, perhaps.

DR. ROBERTS: I know they did a treatment by

gender interaction. And I'm sorry, I'm just blanking right now and if that was significant or not. I don't believe it was, but I'd have to get back to you because we do have that information.

DR. BURMAN: Does the sponsor want to respond very quickly?

DR. ARONNE: If I could have the forest plot, please.

So we did look by gender, as presented in this forest plot of placebo-subtracted mean change. And what we see in this is that females do have a slightly higher weight loss associated with treatment than males. But nevertheless, both genders were significantly greater and somewhat dose-related compared to placebo.

DR. BURMAN: Thank you.

Dr. Roberts, do you want to expand on that later?

DR. ROBERTS: No. I think that's what I recall as well.

DR. BURMAN: Thank you.

I think the last question, Dr. Veltri.

DR. VELTRI: Yes. Very quickly, on slides 14 and 15, you talked about some of the lipid effects in the comorbidities. Some of these patients were hypertriglyceridemic and obviously on therapy for that.

Did you see any differences between those on and off antilipid therapy?

The tachycardia I just want to get back to very quickly. In those who had persistent tachycardia over 100, were EKGs looked at, since these heart rates are really vital sign heart rates, to make sure that there wasn't -- that it truly was sinus tachycardia as opposed to an ectopic tachycardia?

DR. ROBERTS: With regards to the triglycerides, as you would expect with weight loss, the effects on the LDL is not quite as robust as what you would see with the triglycerides. If I'm recalling correctly, when you looked at the subgroup with hypertriglyceridemia, who could either have a high triglyceride or be controlled, at least maybe up to two medications. I believe there was also a reasonable decrease of around what you see here. It

wasn't significantly different from what you saw overall in the group.

Then with regards to the EKG data and if it was an ectopic tachycardia, is that -- sorry?

DR. VELTRI: Well, when you see a persistent tachycardia over 100, one of the concerns is, is it truly a sinus tachycardia or is it some ectopic? And so if you have a sympathomimetic drug, it could be causing some kind of arrhythmia.

DR. ROBERTS: Right. I don't know if they did EKGs at every visit, and there certainly wasn't where it was 24-hour Holter monitoring to look at this. So I can't speak specifically if they looked at EKGs when there happened to be someone with an elevated heart rate.

DR. BURMAN: Did you do continuous monitoring EKGs?

DR. GESUNDHEIT: We did EKGs on everyone at entry and study exit. And we did analyze those for potential ectopy, and we did not see an increased rate comparing active drug to placebo in any suggestive ectopic rhythms. The tachycardias from EKG, the few

that were still available, were sinus tachycardia.

The other question was -- oh, continuous monitoring. We did do continuous monitoring during the sleep apnea studies. Those patients, during their polysomnography, had overnight continuous monitoring. And we did not see any -- and we had a placebo group and an active treated group. We did not see any increased ectopy in the patients with continuous monitoring who were on the active drug.

DR. BURMAN: Thank you. Thank you all. There are a few other extra questions, remaining questions, that we'll please bring up this afternoon when there's time.

We will now break for lunch. We will reconvene again in this room again in one hour, at 1:00 p.m. Please take any personal belongings you may want at this time. The ballroom will be secured by FDA staff.

Panel members, please remember, there should be no discussion of the meeting during lunch among yourselves or with any member of the audience.

(Whereupon, at 12:00 p.m., a luncheon recess

was taken.)

A F T E R N O O N S E S S I O N

DR. BURMAN: We'd like to get started. We will start our OPH session.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and the committee in their consideration of this issue before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

The first open public hearing speaker is Lynn MacAfee.

MS. McAFEE: Hi. I'm Lynn McAfee. I'm director of medical advocacy of a nonprofit group called the Council on Size and Weight Discrimination. The council does not take any funding from any part of

the diet industry, including pharmaceuticals, nor do I personally.

I jotted down a few things this morning that I thought were of note that I wanted to talk about, in no particular order.

First I should say what's probably eminently clear. I'm not a diet success. I weigh 455 pounds. That's a BMI of 71. And I'm sure you're going to hear success stories here, and I am really happy for people who are successful at it. But we have to bear in mind that there's a lot more to the picture of any diet drug than who succeeded.

A couple things. When I go to one of these hearings, I have to think of two questions. And one is, would I take the medication that's at the hearing? And the second is, is it a good thing for plus-sized people to take this medication? And in this particular instance, the answers are, I think, going to be different.

I probably would try this pill when it came out. Now, I've taken topiramate before, and I've taken phentermine before, but never together. I had

terrible side effects from topiramate and phentermine. But I'm interested in this whole idea of a low dose. I would take probably the lowest dose and might move to the middle dose. I would not take the high dose. I am not happy with the increases in several different kinds of side effects with that.

Turning to another issue, and that is the indications for this drug, the population they're looking for, is ridiculously broad. And I don't blame the sponsors for this because every diet drug that's come up has done this. And I don't think it's a good idea. This is a huge public health experiment on two drugs that have known side effects already. So I think that it really makes sense to look at the people who have the absolute most to benefit.

What's disappointed me also is we're back to one-year trials on obesity, and this doesn't make sense, and I think we all know that. The history of obesity is that you lose weight for six to eight months -- and this is without medications or with it; some medications do better -- and then after a year, you slowly begin to gain back weight, even if you're

still taking the drug, sometimes. If you don't take the drug, you're going to gain it back real fast in most cases.

So it's very unhappy. I mean, if this drug is really good -- and I know the company thinks it is -- I don't understand why we didn't have a two-year trial so they could show that they defeated that. And I hope they will continue to do trials and look at something two or three years out. I think that's very important.

I probably shouldn't mention this here, but since I have the drug company in front of me, we really have to do something about the cost of these things because I hope insurance will pay for it, but many people don't even have insurance, and many insurances won't pay for it. So I just want to take this opportunity to beg you to keep the cost down.

You did have a very nice completion rate, let me say that. In other trials, they've run around 50 percent dropout, so that's a really nice rate. And it says to me that these drugs did have some effect, considering the side effects they had.

The heart rate issue is a stopper for me right now. I can't get my head around it. I don't quite understand how raising your pulse rate that way and a little drop in blood pressure makes everything normal. And I don't understand -- is that going to go on forever? Is that going to stop? I don't think we know that, do we? Or maybe we do. You people have talked about a lot of stuff today, and for a nonprofessional, it's kind of hard to keep up sometimes.

So I think the effectiveness overall is certainly better than what we've seen. But is it good enough to risk these side effects that we've all heard about this morning, some of which can be even fatal, I understand. And that's what we really need to think about, is enormous amounts of people risking this.

I hate to bring it up, but Fen-Phen. I think we all lived through that. I know I got calls in the middle of the night for a long time from people who had heart valve problems and primary pulmonary hypertension, and really didn't even have that much weight to lose.

You have to know that anorexic and bulimic chat lines and chat rooms were telling each other how to get the drug, even though they were less than 100 pounds, and did get the drug.

Another thing to remember is, this is a 10 percent weight loss. This is not going to make us thin. And that's important. We are still going to probably have most of these comorbidities. Now, they may be better, although I'm not sure. In some of the obesity studies that were mentioned today, blood pressure went down, but after three years it rose back up to baseline, even in those who kept off the weight.

So that concerns me a great deal. We really need to think about we will not be thin. We will not have the same risk profile as people who aren't fat. We're not just temporarily not thin people. We're different, and we have to begin to recognize that.

I also have been talking to a neuropharmacologist in this last week who I hope the FDA will contact who had some real concerns about topiramate, and are researching things now, some of which are in press, that disturbed me. And so I hope

you will follow up on that.

I've had a kidney stone. I don't want it again. So the kidney stone things is a bit of a bother. I wonder if there's some way we can ameliorate that.

There's a lot of stuff going on, and you've already had two hellish days. I just want you to know that plus size people everywhere really appreciate the effort that you're putting out on other behalf. No matter what you decide, we know that you will put your all into it, and we appreciate that. Thank you.

DR. BURMAN: Thank you very much.

Dr. James McKinney.

DR. MCKINNEY: Good morning. I'm Dr. Jim McKinney from National Clinical Research in Richmond, Virginia. Neither I nor the patient to speak after me have any relationships, financial, with this company or any other company.

I was the principal investigator of OB-303 and its extension, 305. You've looked at the data from this study and others, I'm sure, today and before. Today I'd like to put a face with the data

and introduce to you Ms. Gloria Elliott, who is a patient of ours. And she'd like to tell you her experience with the drug.

MS. ELLIOTT: Thank you, Dr. McKinney.

Good afternoon. I am honored to be speaking today on behalf of the Weight Drug Research Study. I am one of the participants who was in the weight loss research on a blind study, but times two years. I am now going to tell you about my experience in the study.

In the first year -- slides please -- in the first year, I lost 42 pounds. My cholesterol went down, my blood pressure went down, and my blood sugar went down. And my hemoglobin A1c went down from 6.7 down to 6.2.

After that, I was able to reduce my blood sugar medication because I am diabetic. I am hypertensive, and I do have hyperlipidemia. So this is a wonderful study for me.

I was taking 1500 milligrams of metformin on a daily basis. And in one year's time, I reduced my metformin down to 750 milligrams a day. I continued

to take my blood pressure medicine on a regular basis and my medicine for hyperlipidemia.

In that first year, which I had never done before and never was able to do because I was too large and too overweight and out of shape -- but in the first year after that study, I did three marathons, a 10K and two 5Ks. And I felt good.

In the second year, I continued into the study. I maintained my weight. I maintained my HbA1c. I continued to do my blood pressure medicine at 750 milligrams. That was normal. My blood pressure was normal. And at the end of that two-year period, I still had my weight down. I even lost more weight, and I felt better. And the study ended in January 2010.

It has been six months since I've been on that study and used those medications. My hemoglobin A1c now is 6. My blood pressure is lower than 110/70; it's around 100/60 right now. My cholesterol is in the normal range. My blood sugar is anywhere in the 90s or in the 80s.

I continue to struggle with my weight,

trying to keep it down, trying to maintain my journey. I'm on a journey right now for healthy eating and exercising.

When the study research drug becomes approved and available on the market, I will be definitely using that drug. I will be definitely continuing to exercise on my regular basis. And I will continue to take my medication until I no longer need it, and I have reached my goal, and I will be thin, on the journey, then the battle of the bulge will be over. I will have made it and I will be a success story. No more blood sugar medicine. No more blood pressure medication and no more cholesterol medication. Only eating healthful and exercising and joining the people who are much smaller, much healthier, and doing much better than I am. I will be there in 2011. Thank you.

DR. McKinney: Thank you, Ms. Perkins.

[Applause.]

DR. BURMAN: Thank you very much.

Kelly Close.

MS. CLOSE: Good afternoon, Mr. Chairman and

members of the committee. My name is Kelly Close. Thank you for giving me the opportunity to come speak with you today.

I'm editor-in-chief of three publications about diabetes and obesity, and they serve patients, providers, and those who research and develop therapies to treat these conditions. Our mission is to help improve patient outcomes by getting better information, the best information possible, about diabetes and obesity to anyone who needs it.

By way of disclosure, various manufacturers, doctors, nurses, researchers, subscribe to our main newsletter called Closer Look. Vivus, the developer of Qnexa, is one of several dozen companies that subscribe to our news service. I don't feel beholden to industry in any way, nor does anyone on my team, nor have I discussed any of this testimony with anyone in industry. Our patient newsletter, diaTribe, is free and does not accept advertising.

So I have a personal stake in my area of expertise. Since I was teenager, I have had type 1 diabetes, which is not associated with obesity, but

I've watched many in my family and broader community struggle with excess weight. Although my father officially died of cancer, we know obesity and cardiovascular disease contributed significantly to his declining health.

Throughout my life, he frequently lost and regained weight, 10, 20, 30 pounds at a time. It's a vicious cycle of desperation, incremental progress, and crushing defeat that I came to recognize from a very young age.

So let us be clear. Obesity is a disease. It diminishes quality of life for more than 100 million Americans, and it is a killer. The key point that I want to make to you today is that compared to other diseases, we are doing very little in our country about obesity today, and it is literally killing us, bankrupting us, and handicapping our lives.

So to make this clear, I would like to share some additional voices with you. Last week, we e-mailed a survey to 2500 of our diaTribe readers who had indicated that they were overweight or obese, and

we shared with them that we would be coming to the advisory committee meeting today. We had nearly 700 responses within 24 hours.

In addition to sharing data on a wide range of health care issues, the respondents wrote in comments like the following one, which I share with you verbatim.

"Please help us." So that's how it starts. That's what they're saying to you. "Please help us." "It is not a matter of my not having self-control. It is not that easy. I have a problem, a very real problem. I have lost weight countless times. I have tried it all, -- Weight Watchers, diet pills, Atkins, fasting, milkshakes instead of meals, Overeaters Anonymous, so many things.

"When I was 13 years old, our family doctor gave me amphetamines and started me out on a lifelong nightmare of losing and gaining. Now I am a 300-pound middle-aged woman with diabetes. I'm not asking for handouts. I need some help. This is a nightmare I cannot wake up from. "Thank you for asking, and please look past my exterior and know that inside, we

are the same."

That's the end. And we are the same. And she and 100 million other Americans in -- 300 million -- 100 million Americans do deserve more attention. And that's what I would like to humbly ask you for today.

Just a couple more details about our survey that I found personally really daunting. So we found in our survey that obese patients, compared to those who aren't overweight, are three times as likely to have heart and circulation problems and nerve damage, two and a half times as likely to have cholesterol problems, and one and a half times as likely to have kidney problems. Twenty-nine percent of the obese patients that we surveyed have depression, compared to just under 7 percent in the general population.

Ninety-three percent of the survey respondents with a BMI greater than 30 -- the definition of obese, as you know -- said that they tried in the past to lose weight for health reasons, but two-thirds report that they were simply unable to keep the weight off for a year or more.

I may feel differently if patients could be helped significantly by their health care providers. So obesity is a preventable disease. Right? You know, we hear that all the time. But medicine is underserving patients with chronic diseases, and obesity is just no exception.

The diabetes patients struggling with weight issues that we surveyed spent an average of only 21 minutes per visit with their doctor over the last year at each visit, and we know that's actually higher than what many patients are able to get.

Patients surveyed also told us that an astonishing 26 percent of their doctors did not talk to them about their weight, 36 percent of them never recommended they start an exercise program, and only 20 percent of them felt that their doctors were actually able to help them lose weight.

While this is unsurprising, given the lack of reimbursement for doctors' time in our system and given the paucity of tools, it is still incredibly dispiriting to me as an American. So from a patient perspective, the message is a really troubling one.

In addition to patients who feel overwhelmed, many doctors have given up.

What can be done?

[Time expired.]

DR. BURMAN: Do you have a quick -- the microphone is off. Do you have a quick closing comment?

MS. CLOSE: I do. Thank you, Mr. Chairman. I just wanted to say that on the medical front, we badly need more and better options. The drugs need to be safe and effective, but they don't need to be perfect as much as they need to be available if we're going to curb the epidemic.

I would just close by saying that in an idea world, exercise, diet, and education, which we all want more of, would turn a flabby nation into a healthy one. But because we don't live in that world, please work to give obese patients more help, and I ask health care companies and their regulators to be relentless in looking for some alternatives.

Thank you very much for the time and the opportunity to speak with you today.

DR. BURMAN: Thank you very much.

Dr. Apovian?

DR. APOVIAN: Thank you. My name is Dr. Caroline Apovian, and I am representing the Obesity Society. Obesity is a chronic, relapsing neurochemical disease, and as the root cause of type 2 diabetes and other medical comorbidities, is a major contributor to the public health burden in the United States.

Overweight and obesity is the second leading cause of preventable death in the United States. While a few recent studies have suggested that obesity rates may have begun to level off, still, two-thirds of Americans are overweight or obese, and more than one-third are obese. Moreover, the burden of obesity is disproportionately borne by women and minorities.

The Obesity Society is the leading organization in the United States dedicated to studying the causes, consequences, prevention, and treatment of obesity. The Obesity Society endorses that to reduce the burden of the obesity epidemic, a multifaceted approach is needed. Such an approach

should combine clinical, public health, and policy approaches to the prevention and treatment of obesity.

Pharmacotherapy can be a useful tool within a toolbox of clinical approaches to treatment. We support the use of weight loss medications in appropriately selected patients. The choice to use medication is an individual decision that must be undertaken between clinicians and their patients.

Our position is in agreement with guidelines from medical profession societies such as the American Medical Association and the American College of Physicians, as well as treatment recommendations from the National Institutes of Health.

Because of its chronic nature, the cure of obesity is rare, but palliation is a realistic clinical goal. Weight loss occurs with most treatments, and except for surgery or very low calorie diets, it is usually slow, .5 to 1.0 kilograms per week. Recidivism or regain of body weight is common after a weight loss program is terminated. In contrast to the relatively slow rate of weight loss, weight regain may be rapid.

A regain in weight after termination of drug treatment is often ascribed to a failure of the drugs or other treatment. A more appropriate interpretation is that treatments do not work if they're not implemented, and medications do not work if not taken. This is true of medications for the treatment of obesity, just as it is for medications used to treat hypertension, diabetes, heart disease, or asthma.

Because obesity is a chronic disease and obesity medications must be taken over the long term, safety of these agents is paramount. The Obesity Society Supports the following specific recommendations regarding the use of pharmacotherapy.

All prescription medications for weight loss should be subjected to large clinical trials with enough participants to assess safety.

Weight loss agents should be tested for efficacy in subgroups that include women and men as well as ethnic minorities with disproportionate rates of obesity, for example, African Americans and Latinos. The use of pharmacotherapy in clinical practice should follow established guidelines.

Specifically, weight loss drugs should be prescribed only to patients with obesity, BMI over 30, or to overweight patients, BMI over 27, with weight-related conditions.

Patients using pharmacotherapy should concomitantly pursue intensive lifestyle interventions, as this approximately doubles weight loss.

The use also of other toolbox approaches such as meal replacements, structured diets, structured behavioral modification techniques such as food and exercise diaries, should be used as adjuncts to aid the weight loss.

The Obesity Society urges the FDA to approve safe and effective medications for obesity management. Such safe and effective medications should be eligible for reimbursement by third party payers. Thank you.

DR. BURMAN: Thank you.

Ms. Margaret Pence?

MS. PENCE: I have not been financially compensated in any way.

Thank you for this opportunity to tell you

about my personal experience with this medication. I've struggled with my weight all my adult life, and while there have been periods when I lost weight and managed to keep it at a relatively normal level, it took phentermine to get it off and an extraordinary effort to keep it off, to the tune of a daily six-mile run.

Obviously, phentermine has unpleasant side effects. It made me edgy, nervous, shaky, and breathless. It made my blood pressure high, and I was so talkative that even I wished I would shut up. But that was a price I was willing to pay to maintain a normal weight.

Depending on where you live, it can be hard to get phentermine legally, however, and in spite of what it could do for me, I was never willing to do anything illegal to get it. So I tried everything else that came along, every new diet pill, every plan. I can't imagine how much money I have spent in an effort to control my weight.

But there was always a downside to these products. Either they didn't work at all or they had

side effects I couldn't tolerate, feeling depressed or like I was in somebody else's body or just plain weird. And so I waited until the next thing came along to offer me some hope. And I stayed fat, and I stayed constantly angry with myself.

I guess one important question is, why am I fat? Is it because I'm lazy? No. I was in the Army for 22-1/2 years, and during that time I managed to max my physical fitness test numerous times. I ran my two-mile run in as little as 14 minutes and 4 seconds, and then was disappointed that I didn't break 14 minutes.

Now I'm retired from the military, and with my husband, we take care of our 25-acre horse farm with four horses that produce up to 200 pounds of manure a day, all of which has to be picked up. I work a job. I volunteer two days a week exercising horses for a boarding stable. I carry 50-pound feed sacks. I carry filled water buckets and 45-pound bales of hay. I get lots of exercise.

Is it because I eat too much? Well, the obvious answer is yes. I clearly eat more than my

body needs. But I would have to say I don't eat to excess.

So is it metabolic? You're the experts, but I will say from my experience with horses that metabolism is a possible culprit. If you know horses and horse breeds, you will be aware that some are known as "easy keepers." That doesn't mean that they're really nice horses with great personalities, and they're tidy in their barn habits. That means you don't have to feed them much. Or in other words, they are cheap to keep because you don't have to feed them very many calories.

Unless you feed them what for most horses would be a starvation diet and keep their activity level very high, you will have an obese horse in a very short period of time. Oddly enough, these horses are also well-known for loving to eat.

Unfortunately, I think some of us humans fall into the "easy keeper" category, meaning we need almost nothing to maintain our weight, and it takes only a small number of extra calories to pack on the pounds. Some of us are born that way, and I think

others acquire the condition as they age.

How has being overweight affected my life? I've always been an active outdoor person. In addition, I chose the military as my career. In both situations, you spend the majority of your time with people who are, for the most part, active, physically fit, and who, like most of our society, view overweight people as slightly substandard.

We believe they have no self-discipline, that they're responsible for their own condition. Yes, we think they're gluttons who can't control their eating, and sit around on the sofa watching TV and stuffing their faces.

How do I know that's what people think? Because that's what I think when I see somebody who's overweight. My view is a mirror image of the view held by our society as a whole, and especially by those who are active or in the military.

I don't exempt myself from my condemnation. When I look in the mirror, I see someone I don't have any respect for. I see a person I don't like. I see a person I'm ashamed of. I avoid mirrors, and

cameras, and even my reflection in a window. What I see there causes me to dislike myself, which in turn poisons my relationship with others, even those closest to me.

How did taking Qnexa change that? When I began the trial, I weighed nearly 200 pounds. At the end of the trial, I weighed 143 pounds. I went from a size 20 to a size 10. I was fairly active prior to starting the trial, and I made no effort to change my activity level, but it increased slightly purely because it was easier to move. I made no effort to change my eating habits, but they changed almost immediately upon starting the trial. My brain quit nagging me about food.

Instead of being entertainment, food became fuel. I never thought about food except when it was time to eat. At mealtime I could choose what to eat based on what I knew was healthy and appropriate because my brain wasn't begging me for a taste of this and a taste of that. I immediately became a person who didn't snack between meals and who chose healthier food at mealtime.

I believe the medication boosted my metabolism, but I can't tell you that based on anything I've felt. I had no negative side effects, no jitters, no irritability, no depression, nothing. I felt completely like myself throughout the trial.

On the other hand, I did experience a positive side effect in addition to the weight loss. I have high blood pressure controlled by medication. While taking Qnexa, my blood pressure, which is usually around 125/90, dropped to an average of 105/85.

Based on my personal experience, I believe Qnexa is a tool that will give many people --

[Time expired.]

DR. BURMAN: Please finish. Please turn it on so she can finish quickly.

MS. PENCE: Based on my personal experience, I believe Qnexa is a tool that will give many people healthier lives both physically and emotionally. I strongly urge you to approve Qnexa for use in appropriate individuals. Thank you.

[Applause.]

DR. BURMAN: Thank you very much.

Ms. Aycock?

MS. AYCOCK: Good afternoon. My train travel from and to New York has been compensated.

My name is Erin Aycock, and thank you for the opportunity to speak to you today. I also was in the clinical trial, and I'd like to tell you a little bit about my experience and why I am so firmly committed to the approval of this drug.

I don't have to tell you about the efficacy of the drug, but I lost over 50 pounds during my year and a half-ish on the drug. During that time, I also was accepted to Georgetown University Law Center. I moved to major metropolitan city for the first time in my life. I ran my first 5K.

I experienced the breakup of a four-year relationship. I succeeded in my first year of law school, ending up in the top 25 percent of my class, while enjoying many extracurricular activities and holding down a work/study job. As you can see, my time in law school and during the study has been very busy, very stressful, and intellectually challenging.

I experienced no negative side effects. I didn't experience any depression, suicidal thoughts, trouble sleeping, rapid heart rate, clearly no mental confusion. I did occasionally have some dry mouth, which added to my water consumption, so I considered that a plus.

As a young woman who struggled with her weight, statistically I am likely to struggle with it my entire life. And it feels like a personal failure. For example, when shopping for clothes when I was on Qnexa, everything fit. There was no pulling or tugging. I could wear a bathing suit out in public. It was fantastic. It felt like I had accomplished something amazing. I was proud of myself.

Last week, when I had to go shopping for a dress to wear to a wedding, I couldn't find anything that fit. Nothing was in the right size. And after hours of tugging and struggling, nothing was perfect, but I could make some compromises.

You feel like a personal failure. After all, it's your fault. You're the one who puts the food in your mouth. You're the one who decides how

much exercise to get or not to get. There's nobody else to blame.

That's where Qnexa comes in. It's like instant willpower. I have the ability for the first time in my life to say no. You know, I don't even care if I eat that cookie or not. And that is an amazing power to have as a person who has always struggled with something -- I think I should eat probably some more. I think something else would taste really nice right now.

After I finished with the drug, about six months later I had regained about 90 percent of the weight that I lost. And now I am in New York. I am at an expensive gym. I have a trainer. I am a member of Weight Watchers, and under a doctor's supervision, I am on phentermine again. And not only is all of that incredibly expensive, but it's still so much harder to lose weight that way than it was on Qnexa.

I know that there are concerns. I didn't feel any of them. And I would do anything to be back on this drug. It comes down to help. Qnexa is help. We need help. I need help. Please approve this drug.

It changed my life, and it can change millions of lives. Thank you.

[Applause.]

DR. BURMAN: Thank you very much.

Mr. Nadglowski?

MR. NADGLOWSKI: Good afternoon. My name is Joe Nadglowski. I'm president and CEO of the Obesity Action Coalition, commonly known as the OAC. I have no personal financial relationships to disclose. The OAC is a 501(c)(3) charity, primarily consisting of members like myself who are somewhere in their struggle with their lifelong struggle of obesity. We also have professional, organizational, and corporate members, but today's applicant is not nor has ever been a member.

I will defer most of my comments to OAC's written remarks. I think many folks have already shared some of the sentiments I believe in. But I did want to emphasize two points. The first is a caution, one that I'm not 100 percent sure is actually necessary but I'll make it just in case.

One of the most challenging aspects of

living with obesity is the obvious bias, stigma, and discrimination shown against those who struggle with their weight. But that bias is not limited to just those who struggle. It's actually shown against any intervention or treatment necessary.

Too many people believe obesity is solely a personal failing and a personal responsibility, and no treatment, no matter how safe or effective, is acceptable. I'd ask the committee and the members of the audience to reject this bias. Please evaluate this obesity treatment as you do the treatment of any other serious medical condition.

Then secondly and finally, I'd like to remind the committee that while obesity treatment can be effective, it's awfully difficult. I think lots of people have shared their stories about that today. But the reality of this is a lot of that has to do with the fact that the toolbox is empty. We do not have that many safe and effective tools to treat obesity.

The public needs those safe and effective tools, and that's why your work as a committee is so

very important. You have the work today, and then the work coming in the coming months.

But think about it. The reality is, if we can address both sides of the equation with obesity, meaning both prevention and treatment, and with the commitment to prevention being made in this country right now, if we have an expanded toolbox and access to a wide range of treatments, we finally will be able to put a dent in the prevalence of the obesity epidemic. Thank you.

DR. BURMAN: Thank you.

Dr. Wolfe?

DR. WOLFE: Thank you. Given the literally insatiable appetite of doctors and patients for new drugs as a quick fix for obesity -- understandable -- there's every reason to believe that, if approved, a combination like this will be used by millions over long periods of time, dangerously far beyond its labeling indications. Because of a long list of safety reasons, this drug should not be approved.

Few drugs act on as many different sites as topiramate, including GABA receptors, voltage-gated

ion channels, aquaporins, which are proteins regulating flow of water, and carbonic anhydrases. That explains the therapeutic effects for seizures and migraines as well as some of the adverse effects.

A few examples include acute myopia secondary to angle closure glaucoma; cognitive impairment; kidney stones; metabolic acidosis; oligohidrosis, decreased sweating, and subsequent hyperthermia; suicidal ideation; and teratogenicity. Phentermine also is very active, acting on adrenergic receptors, and I'll talk about that in a minute.

With such a combination of highly active agents, unintended but predictable effects are guaranteed.

Is this acceptable?

Vivus only conducted trials lasting one year, as mentioned Lynn McAfee. This is unacceptable. More than other drugs, diet drugs, with their potential for long-term use, should be accompanied by long-term safety date of at least two to five years. We know that some patients may take diet drugs for a long time because when they stop, they usually suffer

recurrent weight gain.

As would be expected of an amphetamine and an anti-seizure combination like Qnexa, there's a long list of serious effects. I've gone through some of these. Eighteen percent of high dose subjects withdrew due to an adverse effect, compared with 9 percent for placebo.

In the area of metabolic acidosis, high dose patients experienced 12.8 percent of this decrease below bicarbonate of 21 versus 2.1 for placebo. What if the patients also had diarrhea, abused laxatives, or suffered chronic kidney disease? The acidosis would get much worse.

Long-term sequelae of acidosis are serious and dangerous, include nephrolithiasis. By pooling phase 3-treated subjects, almost 1 percent of treated patients, 22 out of 2,201, had nephrolithiasis. If the drug reaches one million people, it could reach millions more; 10,000 people would get kidney stones.

Is that acceptable?

It was hypothesized that adding an amphetamine to topiramate would negate some of the

negative cognitive effects. That just didn't happen at all.

Psychiatric effects. As previously mentioned by a couple of speakers, in the meta-analysis, the pooled meta-analysis by the FDA, topiramate had a statistically significant 2.5 to 3 times greater odds of suicidal ideation than placebo. It was the highest of all the drugs that had a statistically significant endpoint. And in the clinical trials, 7.7 percent of the high dose versus 3.4 percent got depression.

The teratogenicity has been discussed in depth. It would be the only pregnancy X category drug approved by the FDA if it was approved, and I agree with the FDA's findings that there's a high likelihood of exposed pregnancies in this drug.

It's particularly a concern because of what the FDA said was a repeated pattern of craniofacial congenital malformations in animals, U.K. pregnancy registry, North American, and the AERS database.

Four MIs showed up in the treatment group, none in the placebo. This is a drug with powerful

adrenergic effects, the phentermine part. It's interesting the study proposed is following approval, not before. If we are really concerned as we should be about this, the company should agree to do a study before it's approved, not afterwards.

In sum, this is not a novel therapy. It's a repackaging of two old drugs, each of which has substantial dangers. For many reasons, including the risk of off-label use, the drug should be rejected.

Perhaps one of the most important studies relevant to today's decision not discussed in the briefing package or this morning was a randomized placebo-controlled trial of topiramate controlled release for overweight and obese patients with type 2 diabetes. The treatment group underwent 16 weeks of therapy, up to a dose of 175 milligrams a day.

The investigators found that the cognitive/ psychiatric effects were similar to those with Qnexa, namely, higher rates of anxiety, memory difficulties, and insomnia. They concluded that the CNS and psychiatric adverse effects of topiramate CR makes it unsuitable for the treatment of obesity in diabetes.

We couldn't agree more strongly. This study was published in 2007.

DR. BURMAN: Thank you very much.

The open public hearing portion of the meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

It is 1:42. We're going to go till 2:30 in this portion, before we get to the questions. We will now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

We will take some of the individuals who had questions earlier that were unasked.

Dr. Flegal, I believe you had one?

DR. FLEGAL: Yes, thank you. I have a question about the diet and exercise component of all these trials. This is a request for approval in conjunction with diet and exercise.

My question was, are there any data on diet and exercise activities or compliance? Are there any changes in diet and exercise behaviors during the course of the trial? I notice that it looks like the weight loss tends to start plateauing around, I think, week 40. Is that possibly due to some changes in diet and exercise behavior? Do we have any data at all on this?

DR. BURMAN: Dr. Flegal, who would you like to answer that question? Who are you addressing it to?

DR. FLEGAL: Well, I guess the sponsor.

DR. BURMAN: The sponsor. Okay.

DR. FLEGAL: Sorry.

DR. BURMAN: Would the sponsor like to respond?

DR. GESUNDHEIT: Yes. The program that we used throughout the trial is a program called LEARN, which is an abbreviation for Lifestyle, Exercise, Attitudes, Relationships, and Nutrition, and this was used in all the studies within the program. It was developed by Dr. Kelly Brownell at Yale University.

It involves a 12-lesson program, and at each visit -- the visits were monthly -- there was essentially one lesson given in the program.

It provided a structural framework for lifestyle modification, and it focused, as you might expect, on three basic areas of nutrition, exercise, and behavioral change. In it, there was individual goal-setting, individual self-monitoring. Patients were, for instance, given food diaries, mostly for the purpose of reinforcing the notion that they had to abide by their diet and try to reduce their caloric intake by about 500 calories per day.

The program was put into place in part to ensure that all subjects, whether on placebo or an active drug, had a constant lifestyle intervention program so that it would negate any individual site variability.

In the program, here are some of the nutrition goals. One is to reduce caloric intake, as I mentioned, by 500 kilocalories per day; to reduce dietary fat as a percent of total calories; reduce portion size; but to have it be balanced nutrition.

We didn't want, as I mentioned earlier, for patients to have low-carbohydrate diets for fear that that could induce ketogenesis. And as well, as part of the way to engender the right eating patterns, to establish times and places to eat, decrease snack foods, et cetera. I mentioned the use of a food diary.

We also gave out pedometers to help patients establish personal activity goals so that they would measure and try to increase their daily activity. And the goal was, again, to increase activity each week. And the emphasis wasn't on crash improvements in fitness, but rather to moderately increase other activity consistently.

Also as part of the LEARN program is a method to try to encourage behavior modification. And some of the speakers spoke to techniques in their own personal attempts. The subjects were asked to identify eating triggers, which can be barriers to change; to change their eating behaviors; find triggers and chains of activity that might lead to eating and try to intervene and interrupt those;

establish new habits; and set realistic goals so that they wouldn't be disappointed by their inability to keep on track and feel successful in their weight loss program.

So having said all that, we had a weight loss of about somewhere between 1 and a half and 2 and a half percent in the placebo subjects. The one study that had a somewhat higher weight loss was the sleep apnea study, and I can't explain why. That was more on the order of 4 to 5 percent.

DR. BURMAN: Thank you.

DR. GESUNDHEIT: Okay. I'm sorry.

DR. BURMAN: Thank you.

Did that answer your question, Dr. Flegal?

DR. FLEGAL: Thank you. No, it didn't. My question was, really, do you have any data on the compliance of the people in the trial, like are you monitoring their diet and exercise in some measurable, quantifiable way? Is it different over time during the trial, or different between the different arms?

DR. GESUNDHEIT: We encouraged this activity, and we had the nursing staff or the

personnel at the sites monitor. But the only formal instrument we have would be the quality of life instrument, the weight-associated quality of life instrument, which did show statistical improvements in the patients who lost weight on their activity level as they reflected in a recall instrument. But we don't have hard data to document those outcomes. It's more from the recall instrument using that quality of life tool.

DR. BURMAN: Thank you.

Before we go to the next question, the sponsor did answer a question before that they asked me to read, which I'm happy to do, which was relating to Dr. Goldfine, your question from the panel regard beta blockers during the one-year program.

For Qnexa on top dose, there were 38 people, and 2.4 percent were on beta blocker. Placebo was 42 people with 2.7 percent on beta blocker. Subjects taking beta blockers at any time in the one-year program top dose of Qnexa, 219 people, was 13.9 percent on beta blocker versus placebo of 226 people at 14.5 percent.

We'll now ask Dr. Cragan for --

DR. KAUL: Dr. Burman, can I just follow up on that information?

DR. BURMAN: Sure.

DR. KAUL: I think it's important to know what the dose was as well, not just the prevalence of the use.

DR. BURMAN: The dose of the beta blocker and the type?

DR. FLEGAL: The actual question was whether or not the change in beta blocking dosing might have been related to the change in heart rate.

DR. BURMAN: Does the sponsor want to respond to that? Please keep your answers short so we can get to the other questions.

DR. GESUNDHEIT: We can determine dose. I don't have that information. The reason we looked at the prevalence was just to make sure there wasn't any confounding. And what we observed in those data was that the patients who are on Qnexa had about the same use of beta blockers, so suggesting it wasn't -- we didn't mitigate the heart rate effect by having them

on greater percentages or more patients on beta blocker. The percentages using beta blocker overall, and then starting beta blockers anew, was roughly equivalent between the active and the placebo groups.

DR. BURMAN: Thank you.

Dr. Cragan? Oh, I'm sorry. I thought you had a question.

Dr. Morrato?

DR. MORRATO: Thank you. This is for the sponsor. It is a question we weren't able to get to earlier today.

I think you've done a very thorough job in measuring the efficacy assessment, and it's my belief, though, that we should be applying the same scientific rigor that we do in the clinical development program for also defining and evaluating the risk management program. So I have a couple of questions regarding that information that was shared and described.

The first question relates to your specific -- if you can elaborate further on your specific research plan for developing the REMS components that you described in the medication guide.

So, for example, have you conducted any research to date? If so, what have you learned? How are you assessing comprehension of the medication guide, memory of the recommendations? What are you using to evaluate its endpoints in terms of behavioral intent following the medication guide? And have you incorporated learning from other REMS programs that are trying to deal with the issue of pregnancy in terms of not just having written recommendations for "Please don't get pregnant," but actually trying to see those behavior changes, which are extremely challenging?

That's the first question.

DR. BURMAN: Do you want to respond to that?

DR. GESUNDHEIT: I'd like to invite Dr. Stemhagen to address that issue. She's a specialist in risk mitigation programs.

DR. STEMHAGEN: Thank you. I'm Annette Stemhagen. I'm an epidemiologist at United BioSource Corporation, and I've been working in the area of risk management and working on risk management in REMS programs for more than 10 years.

I think your first question is in terms of the tools, and there's a very planned assessment for the tools before they go out into the marketplace. And of course, all this will be discussed with the FDA in terms of the actual content.

But typically there is first qualitative testing. The medication guide is tested to be sure it's sixth to eighth grade reading level so that it will be understood by the general population. And that's done also with qualitative testing, and then there's some quantitative testing as well. Similar kinds of processes occur with the tools, again, to make sure that the patients will understand them.

Then part of a REMS, in any REMS, is a requirement for assessments after it's in place. And that's going to include, as described in the briefing book, quantitative testing, knowledge, attitudes, and behaviors surveys of patients and of health care providers, including prescribers and other ancillary health care professionals, as well as the long-term phase 4 study that the details are still to be worked out on that.

DR. MORRATO: That answers part of it. I think it's just very hard, as a committee member, to assess the sufficiency of the plan when you only have about seven pages out of 300-some-odd pages that talk about all the data, and yet we really don't get to see the actual research plan and timing.

So, for example, in the risk management evaluation, I know you mentioned that the company will aggressively advocate in terms of the pregnancy; I think is what you were referring to, in those guidelines. And yet we have no metrics as to what does "aggressively advocate," what is the planned reach and frequency that you might expect in terms of promotional launch materials that you're applying also to here in terms of the promotion of the safety?

There's no real -- I know surveys, and I think that's a very good idea. But there's no specificity as to when the surveys are going to occur relative to launch; what are the populations in which. And so it's that kind of detail that I think would be more useful, especially since there's much experience that indicates that we all have good intentions when

drugs launch, and yet you don't really have the information you'd like to after launch.

I know we don't really have a lot of time to go into that. But it makes it very difficult to react to the questions that we have to as a committee when we don't have some of that specificity.

DR. STEMHAGEN: Sure. That's understandable. A lot of the materials are still in development, and they will be discussed, of course, with the FDA. And that all requires approval.

With a REMS, the minimum assessment time period is 18 months, three years, and seven years after approval. And so that will be the minimum evaluation time points for at least the surveys. And then, as I said, there'll be also the study, and part of the value of the study will not only be looking at effectiveness and safety, but it can also be used to actually look at how some of these tools will be used.

So if I can have that slide. The slide is the various types. Of course, also, spontaneous adverse events will be reported and evaluated to look for any of the issues.

Some of the materials that will be included will be things that have been used in other instances. We're looking at things, for instance, like the FDA contraceptive guide and things like that. We will determine, again, whether those will be part of the program.

DR. BURMAN: Thank you.

Dr. Morrato, did you have another question?

DR. MORRATO: She anticipated the second one, which was on the evaluation. I'll make a couple of points.

You also mentioned that you're handing out the PHQ-2 assessment as a tool to help with the depression/suicidality, I think, and mitigation; as well as looking at methods to look at the med guide distribution and how that's done; as well as measures, I believe, that relate to whether or not physicians have really done the education program, I think online, and linking that in with prescribing behavior.

So have those kinds of components, in terms of the research of how you're evaluating each of that, been well-defined yet, either?

DR. STEMHAGEN: Again, a lot of that is still being worked out. The PHQ is going to be a tool provided to physicians to use. It's not, of course, a requirement, but there'll be information for the prescribers and other health care professionals on exactly how to use that kind of tool.

So there's a communication plan for health care providers. The med guide, of course, is for patients, and there'll be some other patient materials. And I'm sorry, I think you had another point.

DR. MORRATO: Yes. The third one was I think you had a nice idea, which physicians could go online and get education, I think, or some sort of component.

DR. STEMHAGEN: Oh, yes.

DR. MORRATO: And I was trying to understand how you're linking that information with -- it sounded like with their actual prescribing. So in other words, there would be a feedback loop that if a physician is prescribing this but they haven't shown up, I guess, online with having seen the training,

that there would be some feedback to make sure that they did. And I wasn't sure the details on that. It was only briefly described.

DR. STEMHAGEN: So because data are available through market research and other types of data, we'll know who all the prescribers are. And the online education, again, people will sign up for that. It's not a requirement.

But we'll be able, then, to do matches on that and look for physicians who are prescribing who have not, as far as we know, done the education -- it's not a perfect match because other people can do it -- and then send outreach to those people. That is part of the plan.

DR. MORRATO: And will that be done as you're launching or only at 18 months and five years and --

DR. STEMHAGEN: That will be ongoing. That's going to be an ongoing plan. Typically, also, the medication guide and the communication plan are not just issued once at the time of launch, but they are issued at least annually for the first few years

of marketing so that there's reinforcement of that message as well.

DR. BURMAN: Thank you.

Dr. Goldfine?

DR. GOLDFINE: Yes. You asked one set of them. I have three questions that I hope are very brief.

One, we're going to be asked to comment on the depression scales. We've heard a little bit about the reversibility of the anxiety and attention deficit and memory and language.

What can you tell us about the reversibility of the depression?

DR. GESUNDHEIT: In terms of the time course, Dr. Gadde described the onset of the depression. And what I can tell you in terms of its time course, it's a little bit delayed compared to some of the cognitive changes we showed earlier.

But if we look at the events that were reported in the one-year cohort -- this would be in the entire depression TME subclass -- the median time to onset, as you can see, was relatively early in the

top dose of Qnexa, where we had the most reports. There were 121 adverse events in that class. The median time to first onset was 44 days, and the median duration was about 30.5 days. So it's a little bit more than one visit since patients --

DR. GOLDFINE: When they stopped the drug, did their depression get better? Did they revert back to their baseline?

DR. GESUNDHEIT: Yes, it did. I don't know that I have a slide to illustrate -- oh, here. Okay, I do. I'm sorry.

This shows what actually occurred in terms of patients with depression. And in the majority, actually, they didn't stop drug. In the majority, there was -- for about half of the events, there was actually no change in drug and the patients adjusted to it. In about a fourth or so, the dose was reduced or the dose was interrupted. Then in those that discontinued study, we did have follow-up and took those patients to resolution. And I believe the numbers are about 90 percent of those -- oh, here.

Okay. I'm sorry, I have the slide.

This is now looking at that 28 patients who actually discontinued from the program due to an adverse event in the depression subclass. And we have 82 percent that resolved that we watched, took to resolution. There were 7.1 percent that withdrew and consent was withdrawn, and we're not sure of the follow-up; and then 11 percent where, again, there wasn't sufficient follow-up.

But we documented, in 23 of the 28 who discontinued due to the specific complaint, that the depression did resolve upon study drug discontinuation.

DR. GOLDFINE: If I may, two more quick questions. One is that we've heard some of the patients had gone from the 202 into the 3 study, and that you actually have two-year data.

Can we see the sustainability of weight loss over two years for the few patients who may have been on it for sustained amounts of time, since many patients will be taking it for extended --

DR. GESUNDHEIT: Yes. That study is completing this month, and the data will be presented

to the agency by the end of the summer. The only thing I can tell you, because it's still double-blinded, is that the retention rate in that study is about 85 percent. That's the one piece of data we have on that study. I mean, the retention of patients in the trial. I don't know the weight data. Yes.

DR. GOLDFINE: I understood that. And the final thing is that you really did have a very good education program through the LEARN, as documented by the weight loss even in your placebo group. In the real world setting, it is less likely that there will be such intensive behavioral counseling.

So either do you have plans to educate providers to do the LEARN and distribute LEARN materials, or do you have any information on the use of your drug in a more real world setting where the doctor may simply prescribe it?

DR. GESUNDHEIT: We don't have experience directly in the second category because we did have LEARN as part of our program. But we understand and have a commitment that a LEARN type of program is necessary for this to work optimally.

So we've actually been in discussion with the founder of the LEARN program, and either we will adopt that program or create one of our own that will have the same components to it. I showed this slide earlier, and I think it illustrates sort of the patient-centered approach that we would like to take, which Qnexa is a component. But in order for it to work and bring about the sustainable change in weight that we're discussing as a committee, there need to be key efforts made to improve physical activity, healthy eating, and behavior modification.

The hope actually would be that Qnexa doses could be tapered and potentially we could evaluate, long term, whether patients could adapt the other three components to succeed without drug therapy.

DR. BURMAN: Thank you.

Dr. Hendricks?

DR. HENDRICKS: The sponsor has shown that we know there's a progression in obese patients from no diabetes to diabetes. So you've shown a reduction of the progression rate to type 2 diabetes. As a clinician, I'll also be interested in what happens to

the progression between normal blood pressure and pre-hypertension, and pre-hypertension to hypertension.

I wonder if you generated any data in that regard.

DR. GESUNDHEIT: That's a very good question. We were interested in sort of the categorical type of changes you can see with diabetes because the categories are clearly defined by the ADA.

We didn't do that analysis in terms of patients shifting from hypertension to not being hypertensive. But we would expect, with the mean kinds of blood pressure reductions that we observed, that there would be a shift as well in that type of analysis, categorically.

DR. HENDRICKS: One more question.

Phentermine is categorized as a potentially addictive drug. It's a category IV. And I haven't heard anyone discuss that at all.

Is there any concern, and was there any examination of the patients looking for any sign of addiction or withdrawal?

DR. GESUNDHEIT: Yes. We actually had the

opportunity, by virtue of following the patients after they discontinued, to see if there was any emergence or withdrawal-type symptoms.

Well, actually, the slide I'd like is the one that looks at patients who discontinued active drug but stayed on study, in whom we had adverse event reporting. Let me show you this slide.

So to examine that, what we did is we had the opportunity in the cohort of patients that stopped active drug but were willing to continue to be forward in the study program to look at adverse events that were reported in that group. And in particular, what we were looking for were any kind of reports in the Qnexa-treated subjects who discontinued Qnexa in terms of the nervous system disorder and psychiatric disorders, because that would be the kind of withdrawal symptoms that we would be most concerned about.

What you can see in the placebo patients, in the nervous system disorder we had 6 percent reporting rate of adverse events. In the Qnexa top dose -- these are patients who were on Qnexa top dose,

withdrew active drug during study, but we continued to follow them -- we had a 3.6 percent reporting rate. In psychiatric disorders, the background rate in placebo subjects was a 6 percent reporting rate of adverse events, and then 2.9 percent in Qnexa.

So we didn't see any apparent psychiatric-related withdrawal symptoms in the patients who were studied as part of that program.

DR. BURMAN: Thank you.

Dr. Bersot?

DR. BERSOT: I have a question and then a comment.

Back to the progression of diabetes. The people at most risk of developing diabetes would have been those with impaired glucose tolerance or impaired fasting glucose. And I presume, since people were randomly assigned to placebo and the two Qnexa groups in 303, that the same proportion of people with impaired tolerance or fasting glucose values were assigned to each group.

But do you know that for a fact?

DR. GESUNDHEIT: Yes. That is a clear

confounder, and there were equal numbers with diabetes as well as impaired fasting glucose or impaired glucose tolerance in the two groups.

We specified for the FDA that we'd be looking at glycemic control in the oral glucose tolerance test. But this analysis actually happened somewhat recently, so I'm not sure the division has fully absorbed it; but yes.

DR. BERSOT: And then the other question, related to this, is do you know if, in some way, taking Qnexa affects lifestyle to a greater extent in the people taking the drug than in the placebo group? And that would get back to the question that Dr. Flegal asked about how do you know what people did in terms of lifestyle change in the various groups.

DR. GESUNDHEIT: Well, I think it's a good point because I would guess from the quality of life instrument that as these patients lost weight, they become more active, if that's a lifestyle component, which may have helped them in terms of energy expenditure. But we really didn't collect the data from the pedometer to document increased activity, et

cetera. It was more of a tool to try to encourage that.

DR. BERSOT: I think that would be important to do.

DR. GESUNDHEIT: Yes.

DR. BERSOT: And then my comment is about the laudable goal of educating primary care physicians about doing some kind of lifestyle intervention. I think that's nice for all of us to think that it's going to happen. But the drug companies that have been peddling lifestyle change for lipid lowering for years and years, it doesn't happen. And unless somebody pays the primary provider to hire someone to educate their patients about this, they don't have the interest. They don't have the knowledge. They don't have the time to do it. And it's just not going to happen, despite whatever fine thing you do with Kelly Brownell or somebody else.

DR. BURMAN: Thank you.

We have 20 minutes and we have multiple questions, so please keep them brief, both the questions and the answers.

Dr. Rogawski?

DR. ROGAWSKI: Thank you, Mr. Chairman. I have a number of questions for the sponsor.

The first question relates to the proprietary formulation of Qnexa itself. My understanding is that it consists of an immediate release form of phentermine, but that there's a controlled release form of topiramate.

I'm wondering if there's any scientific information to support the use of this specific formulation because, obviously, we're dealing with a risky combination of drugs, and we want to make sure that the formulation is optimal to minimize the risk and the consequence benefits to the patient.

DR. ARONNE: There was some empiricism with the original OB-201 study. That study did include dosing of phentermine in the morning, with topiramate in the afternoon. It was essentially determined and believed that phentermine being a sympathomimetic, a dose first thing in the morning, the stimulant type of effects would be positive, also anorectic, help with appetite suppression throughout the day.

Then topiramate coming a little bit later in the day, late afternoon, supplying yet additional bolstering for appetite and satiety. And then again, the known side effects of topiramate, although the dose was lower, the side effects would hopefully be mitigated by coming later in the afternoon.

So I think what the results told us that --

DR. ROGAWSKI: But you're proposing that there's an opposing effect in terms of the adverse side effects balancing them out. Wouldn't you then want to have the blood levels essentially match each other rather than be at different times during the day?

DR. ARONNE: Well, the half-life of both drugs is about a day. So you do have a peak level, and that steady state, the peak to trough, is lower.

But we did learn and do believe through the clinical trials, as well as other experience, that the twice-a-day early morning phentermine/later in the afternoon topiramate is optimal. So we developed the formulation, which was tested in 301 for factorial, and essentially looked at the pharmacokinetic

parameters to kind of align with the immediate-release forms of these agents.

So essentially, we confirm we have immediate release with phentermine. The release of topiramate does come 9 to 13 hours later. I think one possible benefit of the controlled release is a slightly lower Cmax, but AUC is nevertheless maintained.

So the formulation was used throughout our phase 3 program, was tested --

DR. ROGAWSKI: You're talking about the topiramate in terms of reducing the Cmax. Is that the idea?

DR. ARONNE: Yes, that's correct. If you notice --

DR. BURMAN: This is an important point, but we have other questions. Could you please be succinct? And we'll move on.

DR. ARONNE: So yes, there's about a 30 percent reduction in the Cmax.

DR. ROGAWSKI: Mr. Chairman, I did have a couple of other questions if there's time.

DR. BURMAN: Please do.

DR. ROGAWSKI: Just following up on Dr. Hendricks' question about withdrawal symptoms, withdrawal symptoms are certainly important, but not a major concern. More important is drug-seeking behavior and abuse liability. And I'm wondering if you have any information about that.

DR. ARONNE: Yes. We have performed an abuse liability analysis as part of our submission. In this analysis, this was one of the factors that was assessed. We did run a search for terms throughout our phase 3 program that would suggest some of these types of behaviors, and those searches essentially came up negative on abuse-type behaviors or adverse events.

DR. ROGAWSKI: And just one final question, then. I'd like to revisit a question that I asked before the lunch break with respect to efficacy measures broken down by sex differences, and the proper term is sex, not gender, differences.

I'm wondering, the results that you showed on the slide, did that indicate that there was a statistically significant effect in terms of weight

loss or other efficacy measures in the male subgroup specifically or was that a trend that you showed on that slide?

DR. ARONNE: Yes. It's my understanding that that's a trend that was observed. But we point it out because there is a slightly lower oral clearance in females than in males, and that equates and aligns with what we see in terms of the weight loss.

DR. ROGAWSKI: So that means that we really don't know at the moment whether the drug combination is efficacious in males?

DR. ARONNE: Well, I think we do. We had 30 percent of subjects in 303 that were males. And we look at the placebo-adjusted weight loss in males across our one-year cohort, and although they were a smaller proportion, they were still in the hundreds. And when we look at the placebo-adjusted differences at the full dose, although it's not as high as females, we're still seeing in the 9 percent and significant placebo-adjusted weight loss.

DR. ROGAWSKI: So that was statistically

significant, the difference? Because it looks like the error bars were overlapping there.

DR. ARONNE: Could we have that slide back up?

DR. ROGAWSKI: For the middle group, certainly not. Right?

DR. ARONNE: Essentially, it's a placebo-subtracted change, so your error bars are --

DR. ROGAWSKI: I see. Got you. Got you. Thank you. I have no further questions.

DR. BURMAN: Thank you.

Dr. Thomas?

DR. THOMAS: Three quick questions. The first one is, from what I read, the phentermine in Qnexa, there's an alternation in the area under curve in clearance.

What is the equivalent dose of phentermine alone to the dose of phentermine in Qnexa? Because my guess is 15 milligrams of phentermine is not the same as 15 milligrams of phentermine in the Qnexa combination.

DR. ARONNE: Yes. We did address that

question. We've performed extensive PK assessment through our program. We were able to essentially associate the concentration of phentermine with the associated weight loss. And looking at our PK results -- could I have the far side analysis of phentermine and weight loss, and the interaction?

We were able to model phentermine as a model therapy for its weight loss and compare that against the Qnexa weight loss.

So when we look at the weight loss associated with phentermine, as represented in the orange line, you can see that on the low doses, shown by 3.75 up to the full dose of top dose of 15 milligrams, which is solid line, the weight loss that occurs with an increasing dose of phentermine.

Through pharmacokinetics, we were able to assess that there was a slight drug interaction that occurred in the presence of the combination. And that interaction resulted in essentially a 31 percent increase in the concentration of phentermine, which is essentially equated with just under 5 milligrams on a dosing basis.

But when we essentially assess that amount of phentermine against the weight loss on a weight loss as a function of dose capacity, you can see, through comparison with the green line, that there's clearly a significant difference, and that the additional phentermine does not account for the efficacy that we see in the combination.

DR. THOMAS: The second question is I'm concerned about the acidosis and bone health. You did bone density studies for fat-free mass and lean mass. Do you have actually bone density data from those DEXA studies? And the second part is, is there any fracture data?

DR. GESUNDHEIT: Yes. We did total body composition using DEXA. And then at the agency request, we went back and asked the technical group to actually look at DEXA-derived total bone mineral content, which is shown here.

This is in about 200 subjects, which were a representative group from the phase 3 program, in which you can see, if you look at the placebo column and then the Qnexa groups, that the overall baseline

values were well matched and that at the end of the one-year period, the mean changes were very small and not statistically different.

There's a nominal change in the placebo group. There's a change of about -4.9 grams in the Qnexa top dose. And that difference was not significant. The p-value on that was .81.

So the second question about fractures is -- I'd have to ask our group to look at adverse events of fractures s if we have any report. I don't have that at the moment, but we can request that, perhaps, during a break and get back to you to see if there are any reports of fractures.

DR. ARONNE: Sure. We can bring that back.

DR. GESUNDHEIT: Yes.

DR. THOMAS: And the third question is really just a quick one about how blood pressure is measured. What I read was after a 10-minute rest period, it was measured once. And how reliable is that when most studies looking at blood pressure would usually have a wait period plus multiple measurements over time to ensure that the reproducibility is not

one single measure?

Since blood pressure is an important factor in this decision, could you give me some data about the quality of blood pressure measurements in the study?

DR. ARONNE: Yes. We did measure blood pressure similar to the method you described. I think the one consideration, this was a secondary endpoint and an endpoint made in consideration of safety probably more than efficacy. And the number of endpoints that we see, and the size of the trials that these endpoints were taken, I think kind of make up for some of the deficiencies and the degree of consistency of the measure itself.

DR. BURMAN: Is that all right?

Before we go on to the next question, let me just raise an administrative issue for the panel. It's about 2:20. We're supposed to take a break at 2:30, from 2:30 to 2:45, and then we'll start the questions.

I'm perfectly happy to just continue to ask questions till 2:45, but I'd like a sense of the panel

to not take a break.

What would the panel like to do? Do people agree to continue? Okay. And if you want some refreshments, then just go.

So with that in mind, we'll go till 2:45, and, Dr. Kaul, you have the next question.

DR. KAUL: Yes. Thank you. Slide 55, sponsor's slide? You know, when you look at all these five endpoints, the endpoints look quite balanced. But what you haven't shown here is the data for the cardiovascular MACE, the conventional cardiovascular MACE endpoint, cardiovascular death, MI, or stroke.

When you look at that, it's imbalanced in favor of placebo 1 to 4. And that 4 is driven by myocardial infarction, which is not the same thing as a non-MI C&E event. You can't weigh them equally. So that's a concerning signal.

But the bottom line is, the portfolio of evidence that you have provided us is too sparse for us to adjudicate the cardiovascular risk. And the only signal that we see is an increased heart rate.

So the question I have for you is what is

the program that you are proposing to address this? And two related questions to the FDA is that if you're able to share the data from another recently analyzed trial with a sympathomimetic -- the Meridia trial, SCOUT, which reported a 20 percent hazard in cardiovascular outcomes when you combine the cardiovascular and diabetic population, was a heart rate or a blood pressure elevation a predictor of risk? Because the only thing we have here is an increase in heart rate. And I want to make sure that that heart rate is not a predictor of risk. And then the second question, I'll follow up.

DR. COLMAN: We're currently evaluating the data from the sibutramine trial, outcomes trial, known as SCOUT. And we do plan to have an advisory committee in the near future. Given that, I hesitate to get into details about what analyses have been done, haven't been done.

DR. KAUL: But you've already shared the data that there is a 20 percent hazard.

DR. COLMAN: Right.

DR. KAUL: And I think it will help the

committee if you could say, of the two variables -- you don't have to go into other details. Of the two variables, was it a blood pressure elevation, which is what you would expect with a more potent mimetic agent, or was it a heart rate? Because if it is the heart rate, then this heart rate signal we see is a serious signal. We have to take it seriously.

DR. COLMAN: Well, the other problem is there's a million ways to do these analyses. This is a trial that went out to six years, so which time points do you use; do you try to average all of them together? Of what I remember, we haven't seen anything that is predictive of MACE from looking at the blood pressure. And I think that's the case with PULSE, but I'm not as sure about PULSE at this point.

DR. GESUNDHEIT: Can I just comment on one thing? I'm sorry. But when you mentioned SCOUT, it's important to know that sibutramine, the agent that was studied there, increases heart rate by an average of about -- and Dr. Colman can correct me -- of about 5 -- it was showing 5 beats per minute, as well as there was an increase in blood pressure. And this was in

Dr. Colman's Annals of Internal Medicine Review.

Whereas in our case, our increase in heart rate is about a third of that by sibutramine, and we have a decrease in blood pressure. And the other part of that -- I'll finish -- is that our increase in heart rate is about 2 percent versus baseline, and our decrease in blood pressure is about 2 to 2 and a half percent. So that's why I think we see this counterbalancing effect.

DR. KAUL: But you do have patients where the heart rate goes up by 5 beats per minute. If I recall, about 50 percent of them do have --

DR. GESUNDHEIT: At one point of 15 different vital signs determinations.

DR. KAUL: Forgive me for emphasizing. The reason why I'm asking this is that the weight loss drugs have a checkered history with regard to cardiovascular risk. And the only signal that we are provided here is this increase in the heart rate. We don't have any data for cardiovascular outcomes to be able to sufficiently adjudicate that.

So I want to hear about what kind of program

do you have to address that. And to the FDA, what is the FDA's feeling on requiring the sponsor to rule out an unacceptable cardiovascular risk? I mean, there seems to be an inconsistency that we have that requirement for diabetic drugs, but we don't have that for weight loss drugs?

I'd like to hear the FDA's position on that because I think that will be important in the afternoon's deliberations.

DR. GESUNDHEIT: Can I ask Dr. Craig Pratt to comment as well, because he studied the adverse events, the cardiovascular adverse events, within our group. And if we could pull up the slide that summarizes the 9 versus 8 events in the cardiac disorders SOC, that would be a good place to start.

DR. PRATT: Craig Pratt. I'm a professor of Medicine at Weill Cornell College, and a cardiologist at Methodist Hospital in Houston. I think that you have brought up a very important point and so has Dr. Veltri. So let's talk about a little data.

The reason that we cast different nets was to try to capture as many cardiac events as possible.

And this one here is different than the one that you mentioned.

Let's go on to the widest one. Could we go to 55?

This was, as you mentioned, a redefinition of MACE. There is a category of sudden death. We have one, on placebo. Four MIs. They came into the hospital with chest pain, had a positive enzyme. One, I think, was a troponin of three. We had four others that came into hospital, were treated the same way, as unstable angina ACS, but didn't have a troponin elevation.

Whether you want to weigh those together or you want to weigh them separately, certainly the sudden cardiac death is probably a thrombotic event. So there just aren't enough events to be able to tell with certainty.

I'd actually like to go to --

DR. BURMAN: Hold on.

Did that answer your question?

DR. PRATT: I'm not --

DR. KAUL: No. The question -- I was able

to figure that out. But what I'm asking is, given sparsity of the data, what program are you embarking on to address this potential cardiovascular risk?

DR. BURMAN: And can you answer that question quickly?

DR. ARONNE: Could we have the outline of the outcomes study, please?

DR. PRATT: I was just going to mention one of thing, and that is there are very few outliers of heart rate that are consistent more than one time in a row. When you get to three or four visits, nobody had a heart rate greater than 100 all the time. So the heart rate issue, I think, has a trial more data than we've been able to present.

This is the trial that is proposed, recognizing that there are absolutely no definite designs yet. But the idea is to look for cardiac events. And there's a commitment from the company, and many people are going to be involved designing this trial.

It will look at hard cardiovascular events, probably MACE or some variant of MACE in cooperation

with the FDA. It will be powered to detect a relatively small difference, and we perceive it'll take three to five years to do that trial.

DR. BURMAN: Thank you.

Dr. Kaul, you had one other quick question?

DR. KAUL: A question for the FDA about is there a position, a firm position the FDA has on requiring to rule out an acceptable cardiovascular risk, and whether that should be implemented pre-approval, post-approval, conditioned on whatever variables?

DR. COLMAN: Well, the short answer is we don't have a formal plan. Obviously, when the diabetes group was generating their guidance document for CV assessment, the question came up that given that obesity drugs, if they're approved, will be used by a large number of patients who have type 2 diabetes, so just from a logical standpoint, it was something that you would want to discuss.

We've had those discussions. It hasn't gotten to the point where we've formalized it in any kind of written statement. I think the question

before us is, at this point, if you think, based on mechanism of action or a signal from the trials themselves, that you'd be concerned about an imbalance in cardiovascular risk.

Then the question becomes, do you think it should be done before or after approval? But we don't have a formal policy for diabetes drugs [sic] right now as we do for diabetes drugs.

DR. BURMAN: Thank you.

DR. KAUL: I mean, this is the dilemma that we are facing here. This is a highly selective patient population with 44 patients with a history of MIs. And you know that cardiovascular disease and the risk factors for cardiovascular disease cluster with the disease condition. And we don't have any information.

DR. COLMAN: Well, let me just take the opportunity, since you've opened up the door. We do have a question about asking you to comment on the PULSE and what you think of it and so forth. So if you feel that this should be evaluated further and to a greater extent, or if you don't feel that that is

necessary at this time, I would urge every one of you to say what you think.

DR. BURMAN: Thank you. We have 15 more minutes for questions, and then we'll go through each in the discussion.

Ms. Coffin?

MS. COFFIN: Yes. I noticed that the participants tended to be -- the typical participant was a woman in her mid-40s. I'm wondering if the committee's being asked to weigh in on any age restrictions on this drug because we know that obesity and overweight is affecting not just adults but our adolescents as well.

DR. BURMAN: I guess I would ask the FDA. As the indication, proposed indication, reads now, there's no age specificity.

DR. COLMAN: The general implication is adults, being 18 and over. And then we'd have pediatric section in the labeling which would specify if we have data for that group and so forth.

DR. BURMAN: Thank you. We have a couple more questions, I see, for the sponsor. We haven't

focused so much on questions to the FDA.

Does anyone have a compelling question to the FDA? Yes, Dr. Heckbert?

DR. HECKBERT: Yes. Thank you. This is a very effective drug, and if it's used -- or, sorry, if it's on the market, I think it is likely to be used by large numbers of people because it is so effective.

So I'm also concerned about its use outside of the intended population and its use for very long periods of time. I'm concerned about its use perhaps without adequate medical supervision, as we saw with Fen-Phen, where diet clinics were set up and people were getting the drug.

Because of that, because it will -- if marketed, it will, I assume, may be used by large numbers of people, it will be used by large numbers of women of reproductive age. And we know from the presentation this morning that despite what sounded like extensive counseling and advice about avoiding pregnancy during the trial, there were 34 pregnancies, and 24 of them were in people using Qnexa.

So my question is, given -- I think there's

some lack of clarity on the possible teratogenic effects here. My question for the FDA is, can you tell us about what's known about the pregnancy prevention programs for drugs that are actually in use now?

The one I'm familiar with is for Accutane, isotretinoin. I wondered if one of you could comment on how effective is that program? And it's been in place, with various iterations, for many years, and there's been a whole lot of effort put into it.

So that to me would represent possibly the best case scenario because the number of women taking isotretinoin is probably smaller than what we would get with this drug once it's on the market, if it's on the market

MS. BEST: Hi. Jeanine Best from the pediatric and maternal health staff.

We have not been completely involved with isotretinoin, our staff. But however, from what we do know, pregnancies do occur, and multiple reasons for that. And the main reason is basic human behavior.

I think part of the problem with some of the

restricted programs, there's never been any research into what type of contraceptives work, what women are willing to use, and there's been research done in other companies that show that a very small percentage of women actually comply with two forms of contraception.

So we actually don't have the research into what works in these programs and what doesn't work.

DR. HECKBERT: Do you happen to know any -- you don't have any numbers, then, about what -- oh, you said a large proportion, the majority of women, do not comply with the program even though they're in the program?

MS. BEST: Well, that's from research done in other countries, that a very small percentage of women actually complied with -- research hasn't been done in the U.S. But research in other countries has shown that a very small percentage of women actually comply with using two forms of contraception in these programs.

I think what happens is they learn to provide the answers that need to be given in order to

get the product. But, I mean, we actually don't know what works. And when these programs were developed, there was never any research into whether it's better to just educate women and teach them how use one form of contraception well, or was there really a need to use two forms of contraception? We don't know the answers to that because that answer has never been researched.

DR. BURMAN: Thank you.

Dr. Proschan?

DR. PROSCHAN: So we heard from one person in the audience who said that after she went off Qnexa, she gained 90 percent of the weight back. And I imagine that stories like that are not uncommon. I'm wondering, does the company anticipate that most people would have to be on this drug for a lifetime, or at least many, many years?

DR. TRAN: Just a quick reminder, if you can refrain from wearing your BlackBerrys or phone to the podium.

DR. DAY: I think the evidence we've heard from Dr. Aronne, obesity is a disease. It's a disease

like cholesterol, hypertension, diabetes. And there will be a need for at least some type of chronic treatment program. It may or may not include absolute long-term use of the drug with lifestyle and diet modification, if that behavior is employed once the weight loss is accomplished.

Certainly there is reason to believe that the drug may either be used at a lower dose or not at all. But I think the assumption is a fair one, that it is a chronic therapy.

DR. BURMAN: Thank you.

Dr. Capuzzi? Let me just say it's 2:37. We have about eight minutes before we go into the questions.

DR. CAPUZZI: My question is quick, actually. It was along the lines of what was already asked. The original labeling by Teva has contraindications of advanced arteriosclerosis, CV disease, moderate to severe hypertension, and that should influence the development program to some extent.

In addition, when you add topiramate, that

might affect the metabolism of that drug and even make it more potent or affect the area under the curve. So both a cardiovascular issue and an arrhythmogenic issue arises, which I think both should be dealt with.

DR. BURMAN: Thank you.

Dr. Weide?

DR. WEIDE: Thank you. I have a couple questions. Two are interrelated, and they go back to the heart rate again.

I just wondered two things. Number one, do you know the percentage of people on drug who stayed above 100 through the trial? And the other part of the heart rate is was there a time where the people who got more than a 20 increase at a particular time during the trial, and was that 20 all early, or was it throughout, or what? But I'd really be interested in the percent that stayed over 100 through the entire trial. Then I'll get to my second one.

DR. GESUNDHEIT: Yes. If we could have the core slide that looked at the patients with heart rates over 100.

I think this will answer it because this

denominator includes all patients in the one-year cohort. So this includes about 3700 patients. And it was uncommon that a patient would have a persistent heart rate over 100. This was defined as a heart rate on two consecutive occasions at any point in the program. And again, heart rate was measured at monthly intervals.

So what we saw was, as I may have mentioned, is that there were 10 patients in placebo who showed two or more heart rates over 100 and 17 on Qnexa at the top dose. But associated with those 17 was an actual lowering of their systolic and diastolic blood pressure compared to the same subjects on placebo. These are simultaneously obtained blood pressures at the time the heart rate was elevated. And then we looked at the impact of an increased heart rate with the lower blood pressure. We saw this rate-pressure product, which actually was lower than it was on placebo.

DR. WEIDE: And my other question has been asked in a couple different ways, and it really reflects my change in thinking over the years about

obesity. And I've come to think of it just like I do blood pressure and lipids, and such that it is a chronic disease that requires chronic therapy.

Every agent that we've seen, when patients go off it, they regain the weight. And I can't think of an exception to that. And you can say, well, they'll change their lifestyle or whatever, but the reality is, when they go off, they gain the weight.

So the real question is when we look at this drug, we have to look at it and say, how safe is it and for how long? Because this is likely a lifelong therapy at some dosage. And so I just feel uncomfortable with a year's worth of data. Two years, you say it's coming soon.

But I'd really like to know because I think this is going to be a lifelong therapy for people. You can hear from the audience that people want this back, and they're going to stay on it. And I think that whatever drugs are going to be available for weight loss, that is what's going to happen. And I think we're going to have to start thinking of it like hypertension and hyperlipidemia, that this is lifelong

1 therapy.
2 So I need a little more from you with that
3 regard.
4 DR. GESUNDHEIT: On the first topic of the
5 heart rate, Dr. Fossa wanted -- he's our -- no?
6 Dr. Pratt wanted to make a comment about the heart
7 rate.
8 DR. PRATT: If we could put that core slide
9 back up, please, that we had with the heart rate?
10 No. I want the one that compares the
11 agency's view of the heart rate to the two times in a
12 row visit.
13 The consistency of heart rates over 100 has
14 been a very important question that's been asked many
15 times. There is an analysis. It's in the core, and
16 it's right here, and you've all seen it. And what it
17 really says is that this is a very scary number of
18 people that increased more than 20 beats per minute.
19 But remember, if you go from a heart rate of 60 to 72,
20 that's 20 percent.
21 So one way to reflect that is to say, well,
22 what about having it twice in a row during clinic

visits? And that's gone down to 4.6 percent here. If you do it three or more consecutive times, or four -- remember, this is out of 15 -- it almost goes down to zero.

So at least in terms of the heart rates at clinical visits, there was nobody in persistent sinus tachycardia for the duration of the trial. We don't have Holter data; that's what we have.

DR. BURMAN: We have two minutes and a few more questions.

You have a quick follow-up for that?

DR. SAUL: Well, I just wanted to address that. But you're only capturing information during the clinic visit. You may be not capturing information in between. What if they have episodes of increased heart rate or blood pressure changes?

DR. PRATT: Let's go to CB-5.

DR. KAUL: And I wanted to ask a question after that.

DR. PRATT: This the only data we have with continuous monitoring, which is the patients that are actually sicker there with sleep apnea. And their

heart rates actually went down over time. And this was continuous monitoring beginning during the trial and at the end of the trial. But we don't have a Holter study, and you're right, there are still missing pieces of information.

DR. KAUL: Well, this is an important question. Otherwise, the FDA would not have posed it as a question to the panel. I mean, there is a signal there. That's the normally signal we have.

So let me ask my final question, with the chair's permission.

DR. BURMAN: If it can be answered in two minutes.

DR. KAUL: I'll try. Because we were shown some information here that appears to suggest that a potential blood pressure-elevating or a heart rate-elevating effect of phentermine is somehow attenuated by the complimentary drug, have you examined closely the interaction between the panoply of diabetic drugs or cardiovascular drugs that can adversely impact this beneficial relationship between the two drugs?

Let me explain. Is there anything that can

attenuate the pharmacodynamic effect of the topiramate, which would then unmask the bad effects of phentermine, or, conversely, any drug that can increase or augment the effect of phentermine, drugs that will be commonly used in the disease conditions that cluster with obesity?

DR. ARONNE: So we're really getting into what we did all our hard work on. So thank you for the question.

Can we have the SSRI interaction for hypertensives?

The only thing I can think of that might begin to address, perhaps, that type of interaction, SSRIs were used in a reasonable fraction, 12 percent of our subjects, antidepressants in general, 15 percent. So we looked at the presence of SSRIs, which one might argue is in a similar class, sympathomimetic type class.

Certainly, if we look at our placebo-treated subjects -- and these are subjects who were either on or off medication, the SSRI -- and then look at the placebo, and you see a similarity in the systolic

blood pressure change throughout the study, maybe a slight bump but certainly nothing significant.

Now, when we look at our Qnexa top dose with 154 subjects on an SSRI, we still see this consistent reduction in systolic blood pressure that we've seen throughout the program, almost every way we cut this data. In every subgroup, every type of interaction, we see this small reduction. And in the presence or absence of an SSRI, we still maintain that reduction in blood pressure.

DR. KAUL: What about antidiabetic medications? What about cardiovascular medications?

DR. ARONNE: Let's see. What do we have -- antidiabetic, I don't think we have anything where we looked at blood pressure per se. I do think it's a fair statement that we've cut the blood pressure data and the heart rate data so many ways, looking so closely at the smallest kind of outlier type of population.

What we're left with when we do that is that we see a small signal in a heart rate and a positive or slight reduction in blood pressure. The two don't

go hand in hand, the blood pressure is consistently reduced, and the heart rate is very small, but it's a consistent increase.

DR. BURMAN: We really have to move on. I think the answer is they don't have a lot of data on the other medications.

Thank you very much. Thank you for the sponsor, and thank you for the FDA.

We're going to now move to the questions. And here's the agenda, the proposed agenda. There are five questions for discussion, with the sixth question being the voting question. And we want to spend the most time on the voting question, and we want to go around after the vote to get everyone's individual opinion.

So that leaves, given the time constraints, 15 minutes for each of the other questions. So we'll start with question number one, which is on the board, which will go until 3:00, and raise any issues that the committee themselves wants to discuss, taking into account the results of the assessments made with the PHQ-9 and the Columbia Suicidality Severity Rating

Scale.

Please comment on the significance of the increased adverse event reports of depression, anxiety, and sleep disorders in subjects treated with phentermine and topiramate. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

This question is open for the committee discussion.

Dr. Thomas?

DR. THOMAS: Over the last few days and in the past, the FDA has gotten a lot of bashing over some of the things that they haven't done. But in the area of rimonabant, I think they did an outstanding job.

They picked up a signal which wasn't very clear early on when the clinical trials were published, and withheld approval for an agent that was approved by many other regulatory agencies, and then subsequently taken off the market for increased suicides, which was a signal risk in a population that had no history of depression, in scores that were

essentially zero for depressive risk.

I am concerned about this issue because there's a dramatic difference between placebo and the highest dose. And there are such a number of dropouts, and depression and anxiety is a cause for dropout, that we really don't have a good signal to say that it's absolutely safe or what type of mitigation steps should be done.

I do have to commend the sponsors because by including people with depression and on antidepressant medications, they made it more like a real world exercise, which is what happens in the real world, is we don't get patients with no history of depression.

Many women, and who probably are most of the trial, tend to have some type of DSM disorder. If you look at data for weight loss programs, 10 to 50 percent of women will have a disorder, binge eating disorder, for a variety of reasons, for whatever makes that up. So I do think it's an important issue that we have to have more data on.

The data on Topamax really wasn't picked up in the meta-analysis that was provided until they had

many more thousands of patients. And the same was true for rimonabant. So with this number, it's really hard to say if there's a safety signal that's really there, or is it something we should be concerned about. And then are there ways of mitigating it if people do get depressed with other agents.

One of the things that was talked about was during the course of the trial that the antidepressants were used in equal amounts. But we know antidepressants also have an impact on weight.

So we don't know which antidepressants were used, was it consistently the same antidepressants, or were there different antidepressants that were used that could have differential effects on weight and also behavior. So the interaction between some SSRIs and the agent in question may be different, depending on which SSRI was used.

DR. BURMAN: Other comments from the committee? Yes?

DR. ROGAWSKI: Well, I would say that doubling the rate of depression in the top dose group is very concerning. However, we didn't pick up an

increase in suicidality risk. The FDA, however, in the aggregate analysis of antiepileptic drugs, did pick up an overall increase in suicidality.

But I think it would be very useful to take a look at that database carefully and see whether, in the group of patients who were taking topiramate specifically for weight loss, whether there was any increased signal.

The reason I say that is because epilepsy itself is a significant risk factor for depression that may not be present necessarily in an obese population. So I think it would be useful to break that out.

So my feeling overall is that we need to look at this in more detail. But I'm not sure that the epilepsy information is translatable in this case. So I personally don't feel that this is a reason for non approval of the medication at this time.

DR. BURMAN: Dr. Proschan?

DR. PROSCHAN: Yes. I thought, actually, the company's slide 69 -- I don't know if we can put that up -- CC-69 -- yes, that was kind of interesting

because this is among people who got depressed. You can see that the mild category in the Qnexa groups increased quite a bit. So I think it caused a lot of people to have mild depression that otherwise might not have had any depression. And then it also increased the pink relative to what you see in the placebo arm.

So if you have moderate depression, then it might have pushed you over into the severe depression. So it seems like it increased depression by a relatively small amount, perhaps, but that's enough to perhaps push you from moderate to severe depression.

DR. BURMAN: Thank you.

Yes? The FDA had a comment?

DR. ROBERTS: Yes. I wanted just to address the last comment about the FDA meta-analysis with topiramate. I told you that we did have some of that information, and I can let you know for the breakdown of people that had the treatment indication for obesity, there was approximately about 3,000 people that were taking topiramate for obesity, and there were three suicide attempts, 12 suicidal ideation, and

in the placebo group treated for obesity, the number of subjects was around 1300. There were no suicide attempts and no suicidal ideation.

Now, for comparison, in the epilepsy group taking topiramate, that was 849 subjects; zero suicide attempts, six suicidal ideations. And again, in the epilepsy group, placebo-treated, approximately 500 subjects; zero suicide attempts; one suicidal ideation. I guess the next group that had the highest number of suicidal ideations were people treated with the treatment indication for bipolar disorder.

If you wanted to know the doses, there were doses that were around 100 milligrams to 200 milligrams and higher, and one of the doses was at -- one of the attempts was at a dose that was less than 100.

DR. ROGAWSKI: So how did the percentages break down there in terms of the use of the drug and the different indications?

DR. ROBERTS: Yes. In terms of the breakdown by proportions, the obesity was not as high as, say, the bipolar disorder ideations. But the

obesity was the largest number of subjects within that group, that treatment indication.

DR. BURMAN: Thank you.

Dr. Morrato?

DR. MORRATO: Since we're also to comment on the mitigation, I know the sponsors had listed that there would be provision of the PHQ-2 for periodic assessment of patients. And I think that's very commendable, just like it's good to give information out on weight loss and that, but I don't think that'll be very effective in actually necessarily being implemented in practice as a way to mitigate risk.

DR. BURMAN: Thank you.

Any other comments from the committee?

Oh, I'm sorry. Thank you. Dr. Henderson.

DR. HENDERSON: I was pleased to see that there was quality of life data. That's been one of my complaints on many of these meetings. And so I commend the sponsor for that. But I see in the quality of life on slide CC-39, social functioning, emotional role, and mental health, they all trend towards favoring the drug. They're not significant,

but that helps reassure me for the mental health evaluation. So I don't see this as blocking approval. But I do see a need for monitoring.

DR. BURMAN: Thank you.

Dr. Goldfine?

DR. GOLDFINE: Yes. On the same point, I actually looked at that, but it actually gave me some concern, because I actually think that in addition to the more specific depression scales, people who lose weight, as you heard from our two select study subjects, usually feel much better. And I was very concerned not to see these improvements on an SF-36. And to me, it suggests that there is additional things being masked in that they don't have the magnitude of improvement I would have anticipated.

DR. BURMAN: Any other comments on this question in the last minute or so?

[No response.]

DR. BURMAN: No? Then Paul asked me to try to summarize our views for the record. And let me see if I can do this and see if there's a majority that agree, and thank you for your comments.

There seems to be an opinion that there probably, or least possibly, is an increased risk of suicidality or at least suicidal ideations in people taking the medication. But we're concerned about or interested in the background population that may be higher in patients with epilepsy and other medical illnesses.

We are also concerned or discussed the fact that in the real -- these studies don't completely mimic the real world situation. But we appreciate the fact that the sponsor did include some other comorbidities in the studies.

We're concerned that there may be interaction with other psychiatric medications and the use of the medication we're discussing, but that hasn't been looked at in a real world situation; and that quality of life benefits seem to be trending toward benefits, but there are questions raised by Dr. Goldfine regarding maybe we would expect those even to be more.

Is there anything anyone would like to modify regarding that? Sure.

DR. ROGAWSKI: Well, I think the issue really relates to the signal that appeared in the FDA meta-analysis of the epilepsy trial data. And there, there was a clear indication that topiramate had an increase in suicidality measures. I don't think, though, that in the data that we saw today that there was a significant increase. It's the depression measures that we're concerned about. Of course, that may translate to suicidality, but I'm not sure that we saw the increase in suicidality per se.

DR. BURMAN: I agree, and thank you, that the suicidality was based on larger doses for different indications.

All right. Then it's 3:00.

Yes, Mike?

DR. PROSCHAN: Yes. Just the end of your statement, I think, is a little bit inaccurate. It said something about a positive trend in the SF-36, and it looks like it's basically null.

DR. BURMAN: From a statistical standpoint, agreed. But there seemed to be a trend, as we saw on the slide.

DR. PROSCHAN: Oh, actually, I misspoke. Never mind.

DR. BURMAN: Okay. Thank you very much.

Let's move on to question number 2 for discussion. We'll go 15 minutes.

Please comment on the potential significance of the increased adverse event reports of disorders of attention, memory, language, and other cognitive disorders, in subjects treated with the medication. If approved, please discuss need for monitoring and possible measuring strategies.

The floor is open for discussion.

Dr. Flegal?

DR. FLEGAL: Yes. Although these parts don't seem as important as the suicidality issues, for example, I think that these are the kind of disorders that might be subtle and hard to pick up or to monitor, but that could affect a really large proportion of people, especially what I would anticipate is a lot of these young and middle-aged women who might be taking this drug, and that this could have a subtle impact that is very, very

widespread, and also could affect some of the behaviors that we're concerned about -- people's judgment, and their ability to follow directions exactly right, and use double-barrier contraception, and so on.

So even though this seems like a smaller issue, I am quite concerned about it just in terms of the possible magnitude in the pollution.

DR. BURMAN: Thank you.

Yes?

DR. ROGAWSKI: I think this is an issue that really deserves some degree of discussion. There's no question that this drug combination -- and it's largely probably due to the topiramate component -- does indeed cause these various adverse events in terms of disorders of attention memory, and language.

I might emphasize that the language one is particularly a concerning one. In my own practice, using topiramate to treat epilepsy, many patients complain of cognitive problems, particularly word-finding difficulties.

So I think that this is going to be a

problem with this drug combination, and it can't be downplayed. However, I think it's also the case that these are largely reversible effects, we believe. And therefore, if patients do encounter problems, if they're appropriately counseled by their physicians and given information that allows them to recognize these problems if they occur, they can come off the medicine and go on something else.

So again, I don't think that this is an issue that would rise to the level of causing us to consider this a non-approvable drug. But on the other hand, I think it's one that can't be discounted and is going to be a problem with this medication combination when it's marketed.

DR. BURMAN: Thank you. And I'd make the comment, to expand on that, that it seems that some of these issues, like cognition, are temporary and perhaps mild, maybe clinically significant for a short period of time. But the issue is if the medication is used in a broader population, how well will these be controlled and monitored?

Anybody else have any -- Dr. Capuzzi?

DR. CAPUZZI: Yes. Just one point. I think there should be some kind of a warning about people who have a dangerous work life, pilots, people that are driving all the time, flying, dealing with electricity, handling handguns, and those sorts of things, at least some caution about that in some way.

DR. BURMAN: That's a good point.

Physicians included?

[Laughter.]

DR. CAPUZZI: Absolutely. We're at high risk.

DR. BURMAN: Dr. Kaul?

DR. KAUL: I might be going here above my pay scale. I don't know anything about this area. But just by looking at the data, it seems like phentermine does not completely mitigate the cognitive adverse events associated with the topiramate.

So the mid dose of the combinations seems to be the most optimal. And there's a common theme here that some of the signals emerge, or I would say most of the signals emerge, at the highest dose, which is also the most effective dose.

So I think we have to pay careful attention to what dose has the most optimal benefit/risk ratio here.

DR. BURMAN: And if I could ask the FDA in follow-up to make sure were all clear, what dose is the sponsor applying for? All three?

DR. GESUNDHEIT: Yes. All three.

DR. BURMAN: Thank you.

Dr. Thomas?

DR. THOMAS: Just one thing to add is there was some conflicting data between the sponsor and the FDA in terms of these issues. The sponsor did say that these were short-term and reversible, or disappeared, but the FDA did have some analysis at 28 weeks that said some of these measures actually stayed, looking at the hazard ratios that are on the left side. So I'm not completely sure all of them are reversible.

The second is the issue about using phentermine to mitigate this actually based on how this was formulated would be surprising because phentermine was used as an immediate release agent.

And there may be some overlap, but one of the advantages of using phentermine early in the day as an immediate release agent would be the fact that the issues you have taking it later in the day, such as insomnia and irritability, would dissipate and allow the topiramate component to actually have effects on feeding later at night, which is one of the problems when people take phentermine alone. They usually have clinically.

DR. BURMAN: Thank you.

Dr. Proschan?

DR. PROSCHAN: Well, in the clinical trial, I heard that there was not any abuse of the medications. But it seems to me that in the real world, that is a real possibility. Someone might very well say, I'll take twice as much and I'll lose a lot more weight.

So I worry about what could possibly happen with some of these conditions if they take a lot more than what they're supposed to, especially since we've heard about examples of psychosis on a higher dose. Of course, I probably should have made this comment on

question one, but I think it applies to both.

DR. BURMAN: Thank you.

Any other comments from the panel regarding these issues?

[No response.]

DR. BURMAN: No? Thank you. Then I will try to summarize for Paul, again with your help. The cognitive issues, in a broad sense, are subtle, not life-threatening, but can be potentially clinically important. They seem to be reversible when the medication is stopped. The implications of applying this medication to a larger population are unknown.

The comment about potential limitations or comments regarding people with certain positions and jobs seems very reasonable, as mentioned by Dr. Capuzzi. And then the question of whether some of these events can be mitigated based on different doses that are given and the time of day.

Any comments or additions to that summary?

[No response.]

DR. BURMAN: Okay. Then let's move on to question three, which is, please comment on the

potential clinical significance of the metabolic acidosis determined by decreases in serum bicarb levels with the medication treatment. If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

The floor is open.

Dr. Heckbert?

DR. HECKBERT: Yes. The company provided information on I think it was 200 people on whom they did DEXA scans. And I think it would be useful, if this were to be approved, to have information on a much larger number of women in particular, but probably men as well, but women would be the area where there would be quite a concern, given what looks like a very small but sustained decrease in bicarbonate throughout the time that people are taking the drug.

DR. BURMAN: And when you're mentioning DEXA scans, you're talking about bone marrow density, looking at bond density and --

DR. HECKBERT: Yes. Bone density.

DR. BURMAN: -- and grams per centimeter

squared rather than a different issue, which is DEXA looking at fat content.

Yes, please.

DR. HENDRICKS: One thing we might suggest would be that bicarbonate levels should be monitored from time to time.

DR. BURMAN: I didn't understand you. Which levels?

DR. HENDRICKS: Bicarbonate levels.

DR. BURMAN: Bicarb? Thank you.

DR. HENDRICKS: To see if there is metabolic acidosis.

DR. BURMAN: Dr. Weide?

DR. WEIDE: Yes. I think the numbers are very small. But what encouraged me was the majority stayed within normal, and it seemed like that they recovered very quickly. The dip was early, right after starting the drug, and then they came back. They also had a number of people on metformin. Again, the numbers are extremely small. But I think I'm not real concerned about the bicarb issue.

DR. BURMAN: If I may, I would make a

comment as well, that the bicarb does go down routinely in people who are on low calorie diets, and it goes down and stays down, usually 17 to 20, and stays that way, and then gradually comes up, depending on the diet and the duration. We don't have pH levels here. All we have are bicarb levels. And we don't know about the long-term effects of this mild acidemia.

Let's see. Dr. Morrato first. Either way is fine.

DR. MORRATO: I'll just add to that. The sponsors had recommended in their risk management plan that long-term clinical effects be evaluated as part of their phase 4 study. So I would concur with doing that.

DR. BURMAN: Please.

DR. ROGAWSKI: Well, I would just comment that topiramate is well-recognized to cause a hyperchloremic non anion gap metabolic acidosis with decreased bicarbonate. And generally, this doesn't cause any problems. There are no clinically significant effects, generally, and it generally

resolves when we discontinue the medication.

But it seems to me that there are some patients who could have a particularly severe acidosis that would be problematic. And therefore, I believe that the labeling should alert physicians to this concern and indicate the kinds of symptoms that patients might have with an acidosis such as GI upset, nausea, vomiting, and all of the other signs that we typically see with acidosis.

The other thing I might comment on is the fact that while I don't believe the sponsor is recommending that the drug combination be approved for use in children, it's believed that chronic metabolic acidosis in children might be more problematic than in adults, leading to stunted growth and rickets and so forth.

So if the drug combination is ultimately going to be directed to a pediatric population, I think this concern has to be addressed.

DR. BURMAN: Thank you. And of course, as was mentioned earlier, other medications, such as metformin might be also indicated for a cautionary

warning.

Dr. Thomas?

Oh, I'm sorry. Dr. Bersot first.

DR. BERSOT: It's already been commented on that topiramate's cleared by the kidney, and in slide 89, the sponsor has said that they're planning on putting something in the labeling about people with renal disease. I believe you ought to have specific creatinine concentration recommendations or GFR recommendations so that physicians will have exact guidance about when to stop the drug or reduce the dose.

DR. BURMAN: Just like we have for metformin?

DR. BERSOT: Right.

DR. BURMAN: Good point.

Dr. Thomas?

DR. THOMAS: Just to add onto this issue about bone, I was a little surprised -- and I only had a quick look at the bone mineral density data -- that there wasn't a bigger drop in the treated groups because the issue of weight loss, you actually do see

a significant drop in bone density.

So I'm not sure what that reason was. We do need to find out what the fracture data is. And this is important for people at the older span of the use of this medication. But to add on to what Dr. Rogawski said was, even though they're not children, peak bone mass is achieved in the 20s. So young adults could have an impact on peak bone mass, which will have an effect many years later in life.

I had mentioned previously that women who are in weight loss programs have a high chance of having a binge eating disorder, which could be considered the use each of laxatives and diuretics, there would be a concern with acidosis that if someone was using laxatives or diuretics, that that could be a serious combination.

So this should be something alerted to physicians in the warning, that you may not be asking about the use of laxatives and diuretics, but it needs to be addressed for surreptitious use. I'm not too concerned about the metformin issues; they've broken down the data with metformin and without. And

metformin lactic acidosis is exceeding rare, much less never anticipated, so I'm not sure that's a real concern.

I agree with the mention about the uses in renal impairment, and you should have clear guidelines so you don't have an issue about a misinterpretation of acidosis from the kidney versus the agent.

DR. BURMAN: Thank you. Good points.

Dr. Kaul? Did you have a question? No?

Anybody else have any issues?

DR. HENDRICKS: A confounding problem is many of the patients that present with obesity have low vitamin D levels. So perhaps, if you're going to follow bone density, we should consider looking at vitamin D levels as well.

DR. BURMAN: Thank you.

Dr. Weide?

DR. WEIDE: I was just going to suggest if we're going to make a creatinine cutoff because of acidosis, that I would probably recommend we choose the same guidelines that we do to metformin to make it easy on the physicians. Otherwise, we're going to

make life extremely difficult, and it seems like a reasonable level.

DR. BURMAN: Thank you.

Dr. Thomas, did you have another comment?

DR. THOMAS: Just one thing to add to the vitamin D deficiency is because of the risk of kidney stones, I'd also wonder about the issue of whether people with a previous history of kidney stones should be using the medication. And though we tend to think of vitamin D as a very safe replacement agent, you may have to use some caution with calcium and vitamin D in some people with kidney stones. So that might be something to take into consideration in the labeling or warnings.

DR. BURMAN: Thank you.

Anybody else on the committee?

[No response.]

DR. BURMAN: Okay. Then let me try to summarize -- and again, please correct me -- that with regard to the effect of low bicarb in metabolic acidosis, as was pointed out, this is a known effect that occurs with the treatment of topiramate of

epilepsy. It seems not to be a major issue in that circumstance, but there are some comorbidities that we should pay special attention to and maybe have a warning. These include anything that causes acidosis, including renal failure; congestive heart failure; GI abnormalities; certain medications, including laxatives; just to name a few. And we can think about that more and give recommendations to the FDA regarding that.

Renal failure, of course, as was mentioned, although we don't have specific quantitative data giving us an idea of how much the creatinine should be decreased in these patients before you have a warning. But it seems reasonable, without that, to use the empiric information from the metformin data.

We're concerned about the effect of acidosis, long-term on fracture risk, and it would be reasonable to do periodic bone marrow densities and to check other factors for bone health including vitamin D.

Any other modifications?

[No response.]

DR. BURMAN: Okay. Then let's go on to question number four. Please comment on the potential clinical significance of the increase in heart rate observed in the medication-treated individuals. If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

This is obviously a topic that we have focused on this afternoon. I would open the floor for discussions.

Dr. Weide?

DR. WEIDE: Yes. I think this has probably brought up the most discussion and is of concern. It's nice to know that the majority of people don't stay up over 100. My concern a lot of the over-the-counter medications result in tachycardia. A lot of them are caffeine-based. You know, it only takes one episode to put somebody into atrial fibrillation. And that's a big deal when that happens for the patient. As we get this into broad use, I wonder what the percentage of atrial fibrillation is going to be. Even though it doesn't stay over a 20-beat increase or more, in a susceptible patient it is going to do that.

The other comment I'll make is that in my experience and my population, which tends to be largely greater than 40 for BMIs, that there is some baseline tachycardia that seems to be related to the weight. I was surprised that their heart rates were as low as they were. So those are my comments.

DR. BURMAN: Thank you.

Dr. Veltri?

DR. VELTRI: Well, obviously, as we all know, the major determinant myocardial (unclear) demand is heart rate. But you have to put in that perspective also that the substrate of the patient is important as well.

Unfortunately, we don't have -- so there is a potential clinically significant ischemic risk here. And there aren't many patients in the subset that we have currently who would be with atherosclerotic disease, although some with risk.

Secondly, I think, as Dr. Rogawski was pointing to, there may be a pharmaceutical reason why we separated these two drugs as far as when their Cmax and Tmax is. We note an atherothrombotic risk;

especially, thrombotic risk is in early morning/late morning. And when you have a sympathomimetic, that can potentiate that.

So where I'm getting at is we have a lot of information about PK here. We probably don't enough information about pharmacodynamics, specifically looking at over a 24-hour-period, especially with first dose effects, where you could have some vasomotor effects, what's happening with heart rate and what's happening with blood pressure, which can be easily done even in the normal population with 24-hour monitoring and electrocardiographic monitoring.

It's very reassuring that the tachycardia really isn't persistent. It's really episodic. But even episodic, frequent episodes can have problems, as opposed to persistent tachycardia, where you could have stunned myocardium, cardiomyopathy, which is typically reversible.

So there's some reassuring information here, but I think there needs to be -- certainly in patients who potentially would have underlying ischemic substrate -- better characterization of the heart rate

and the blood pressure, especially with early dosing.

DR. BURMAN: Thank you.

Dr. Kaul?

DR. KAUL: While I'm very sympathetic to the desires of those who are seeking treatment options for this disease, I'm also equally concerned about the erosion of the public's trust every time we approve a drug and don't get it right the first time, either because the sponsors have not done due diligence and looked for that signal in the right population for where it's supposed to be used in the real world, or just the sample size is not large enough for the signal to be captured.

While I like to applaud the sponsor for doing a properly designed efficacy study, I wish they had equally emphasized their safety study and the right kind of population where it's going to be used.

I agree with Dr. Veltri that we have some pharmacokinetic data. I think I'd like to see some pharmacodynamic data with regards to commonly used drugs, either diabetes drugs, cardiovascular drugs, particularly ACE inhibitors and statins, and also some

over-the-counter drugs, for cold medications and things like that.

I like to see that data before I will feel a little bit more reassured. But I'm reassured that the company is embarking on a study that will address cardiovascular outcomes. I'd like to hear a little bit more details about that study. What degree of risk are they going to rule out? I just saw a sample size of 10,000. Is that going to be sufficient to rule out an acceptable degree of risk? I'd like to hear some more information about that, and I'd like to have Dr. Proschan in on it as well, if the company is willing to provide that data.

DR. BURMAN: Thank you.

Dr. Proschan?

DR. PROSCHAN: Did you want me to -- were you calling on me to answer that or --

DR. BURMAN: Both, if you want to.

DR. PROSCHAN: Okay. Well, I just want to say that there is a tradeoff here, the lower blood pressure in addition to the higher heart rate. And I don't know how people feel about whether they will

offset each other.

The other thing is that I hope that there's no potential significance of the higher heart rate because I have a heart rate of 100 all the time. So I hope it's not clinically significant. That's all.

[Laughter.]

DR. KAUL: Did you want to address the sample size and the treatment effect size that they wanted to rule out?

DR. PROSCHAN: Well, it depends on how big the effect size it. Clearly 10,000 would be enough to rule out some effect sizes and not others. So I don't know how bit an effect size you're looking to detect.

DR. BURMAN: Dr. Rogawski?

DR. ROGAWSKI: Well, as a neurologist, I'm going to leave it to the others on the panel to comment on the cardiac risk specifically. But I'd like to raise a question about a related risk that goes hand in hand with cardiovascular disease, and that is the risk for stroke.

It's well recognized that sympathomimetic agents -- and phentermine is in that category -- have

a potential to increase stroke risk. When I looked into the literature about phentermine specifically, I did find two anecdotal reports of phentermine being associated with stroke.

The concern here is particularly in regard to intracerebral hemorrhage such as might occur in an individual who has an aneurism or a vascular malformation or so forth. I don't think we have enough information to know what the risk might be here, but it's a concerning issue.

I would recommend that the FDA require the sponsor to monitor the drug in a postmarketing surveillance setting for stroke risk. I think this is a significant concern, and indeed, it really could be the problem that Dr. Kaul is raising that's going to give us all a black eye and be real problematic for us in the future.

DR. BURMAN: Thank you.

Dr. Hendricks?

DR. HENDRICKS: There was one paper that addressed this issue about stroke in phentermine. And as I recall, the conclusion was that there was no

increased incidence. There are anecdotal episodes, though, I do agree.

DR. BURMAN: Dr. Capuzzi?

DR. CAPUZZI: Yes. I have one nagging concern. We know that any drug can do anything to any particular person under any circumstances. And here we're starting two medications together at once. And I just wondered if there was some way that the patient could be started on one component, either one, for a while -- it may not be practical -- but then go on to combination. Here we're starting two drugs at the same time on a virgin patient, basically.

DR. BURMAN: Dr. Bersot?

DR. BERSOT: Back to the issue of the clinical trial and the populations that have been studied to date not having included the probably very high risk cardiovascular disease patients who are overweight that are likely to be treated with this drug. And we really don't have any information about the post-MI or post-acute coronary syndrome obese diabetic patient who's likely to be treated with this drug.

We've got the tachycardia signal, perhaps being offset by the blood pressure effect. But I just don't think we know, and the likelihood is great that a lot of these really high risk patients are going to be treated. And we just don't have the information about the risk in that group of patients.

DR. BURMAN: We have a couple of minutes.

Dr. Morrato?

DR. MORRATO: I'd just like to add to that list of high risk patients. Make sure the elderly are included in that as well because there's also very limited information.

DR. BURMAN: As presently construed, there's no age limitation for the medication.

DR. MORRATO: Right. But in terms of the -- what I understood is populations to look at into the long-term trial.

DR. BURMAN: Agreed. Any other comments?

[No response.]

DR. BURMAN: Thank you for that active discussion. Again, I will try to summarize for Paul and for the record, and please correct me.

With regard to heart rate, I think there's serious concern on the panel regarding many issues, which include most patients. On one hand, most patients don't have a pulse that stays over 100 throughout the majority of the study.

We are concerned about the long-term effects of high pulse rate, including possible association or inducement of atrial fibrillation and other cardiac comorbidities, such as congestive heart failure.

It was noted that obese patients frequently have a high heart rate to start out with, although they didn't necessarily in this study. Studies should look at continuous heart rate, not just periodic or intermittent.

We're concerned about the pharmacodynamics of the relationship of the medication with other medications, including those commonly used to treat diabetes, as well as those commonly used to treat cardiovascular disease, such as statins and ACE inhibitors.

We are concerned about using the medication in various populations, including obese diabetics,

including patients with ischemic heart disease and other cardiovascular disease, each of which needs further study.

We do want a cardiovascular study, and we're interested in the number of patients and get more details regarding the cardiovascular study that is going to include 10,000 patients.

We're concerned about the risk of CNS abnormalities and strokes that are higher in patients with diabetes and heart problems, as well as patients on similar medications. And we also are concerned about the elderly.

Any additions to that brief summary?

[No response.]

DR. BURMAN: Okay. Then let's move to question number five, which is, given the doses of topiramate in phentermine/topiramate, please comment on whether you believe the medication poses a teratogenic risk to the target population for weight loss. If you believe it does pose a risk, please comment on how this risk should be managed in women of childbearing potential if the medication is approved.

Dr. Cragan?

DR. CRAGAN: Yes. I had two comments. I think that the information on the effects of topiramate in human pregnancy is evolving. There are monitoring mechanisms out there collecting data, ongoing.

The potential concern about a reduction in fetal weight is a very recent one that's been raised, and needs to be further clarified in other data sets. Hopefully those will be able to give us some information, perhaps, about whether those effects are dose-related.

So the relative risks that are being talked about are moderate. They're along the lines of threefold increase. And I think for a woman who's had an inadvertent pregnancy exposure already, the absolute risks are probably fairly small and counseling can be fairly reassuring.

But I think for a woman who has a seizure disorder that topiramate's the drug that really will control her seizures, the benefits probably outweigh the risks that might be out there. But I'm not so

comfortable saying that's the case for a drug that's likely to be marketed for a very common exposure, where there are a log of reproductive-age women who will be likely to take it, and probably a large number of inadvertent pregnancy exposures, I think.

There have been enough questions raised that I'm not real comfortable with the state of our knowledge right now, going ahead with that. And I say that even with the acknowledgment that obesity is associated with adverse pregnancy outcomes, and may be associated with some individual malformation risks.

The other comment is that if the drug's approved, I agree that monitoring pregnancy exposures and outcomes is critical in the postmarketing arena. And I would encourage the company, if they do that, to look at combining with the existing mechanisms that are out there. And there are programs that are already monitoring topiramate. Motherisk is one.

I don't know whether the North American AED registry would be willing to expand to include an indication for weight loss, but I think it's well worth talking to the PI about that because I think

collecting information through similar methods and case definitions and such will really facilitate the comparisons of this drug with the other preparations.

DR. BURMAN: Thank you.

Dr. Weide?

DR. WEIDE: Yes. I think it's very difficult. We had, really, two different levels of risk by the Motherisk and the FDA using two different basic comparison groups.

While I tend to believe one more than the other, I'm also swayed a little bit by the recurrence of cranial abnormalities. And I think both groups would agree that when you see the same abnormality over and over, then it raises your level of concern a little bit.

I think, although I'm not quite sure which control group is the best, the fact that we're seeing similar defects raises my level of concern more than it would otherwise. So I would say this shouldn't be used in pregnancy. We need to follow up pregnancies in people with Topamax and get more information. But it certainly raises my level of concern.

DR. BURMAN: Thank you.

Dr. Proschan?

DR. PROSCHAN: Yes. I think the evidence that has been presented so far doesn't really show a strong signal that there's a problem. But I think that evidence is -- there's really not that much data. And Dr. Gesundheit mentioned that the confidence interval for the relative risk is about a half to about 2. And so ruling out a doubling is not really that convincing. So there could easily be a fairly large increase that would be consistent with that data.

So while I didn't see any strong evidence, I think, as Tom said yesterday, absence of evidence isn't evidence of absence. I don't think there's enough data to really make a determination about whether there's a problem or not.

DR. BURMAN: Dr. Rogawski?

DR. ROGAWSKI: Well, I believe that topiramate does pose a teratogenicity risk. As a class, antiepileptic drugs are known to be teratogenic. And we don't know why this is, but it

could relate to the basic actions on excitability mechanisms that they have.

I think the fact that the doses in this particular product are low does not really provide much comfort with respect to teratogenicity risk because we know that in some cases, teratogenicity risk can in fact be dose-dependent. In other cases, it's an idiosyncratic risk where there is no safe dose level, and it might be related to a specific genetic susceptibility of the fetus.

So I'm certainly concerned about this. And clearly, the drug combination should be contraindicated during pregnancy for the reasons that the FDA has described. There should be a pregnancy prevention plan, and a pregnancy registry should be instituted.

I think it should actually be separate from the North American AED registry because it really needs to have a control group that's adequate so we can find out an answer whether these low doses are indeed teratogenic.

I might add sort of as a footnote that I'm

less enthusiastic about the milk-only lactation study that was described in the briefing documents, but we haven't actually discussed yet today.

I think it would be maybe academically interesting to know if it's excreted in the breast milk. But we really don't -- even if we had that information, we wouldn't know what a safe level in the breast milk would be. So unless the breast milk was completely free of both components, we wouldn't really be very much further along. And I think it's unlikely that it's going to be completely free of the two drugs.

So my recommendation then would be that the drug should not be used during breastfeeding.

DR. BURMAN: Ms. Coffin?

MS. COFFIN: You were reading my mind. I do agree with -- this is my biggest concern coming in, that this would be a drug that's highly attractive to women of reproductive age, and so the birth defects and the labeling it category X I'm right behind. I would also put in some warnings or some kind of indication until there is any research at all on

nursing moms as well.

DR. BURMAN: Thank you.

Dr. Heckbert?

DR. HECKBERT: Yes. I agree with the comments of Drs. Cragan, Proschan, and Rogawski that I'm concerned about the teratogenicity here even though we don't have a definite answer. And I think my concerns are such that I would recommend that we really need to know more about the teratogenicity before this drug goes on the market rather than finding it out after it's on the market.

DR. BURMAN: Thank you.

Dr. Morrato?

DR. MORRATO: Yes. I want to echo Dr. Heckbert's point of view as well. I was just doing some back-of-the-envelope calculations. If we take some conservative market estimate as to how many women are going to be exposed to this, in the materials that they share there's about 9 million bariatric surgery patients a year. There's about 6 million on phentermine.

If we just assume out of that, which is

really the high risk population, that this is being claimed to want to market against, let's assume one million women. And let's assume that we are not able to, in the real world, achieve any better or worse than what they saw in their clinical trials, which was about a 1 percent pregnancy rate, if I understand right.

You know, we're looking at 10,000 pregnancies in just this select population that we're feeling that the benefit and risk makes sense. If the drug is really used as broadly as we think it might be, then you have a much larger exposure in numbers of pregnancies. And as one said, I think in the open hearing, no one wants to conduct a large public health experiment on the population.

I think we need to have a better sense of really what the risk is or constrain the use of the product so it's really among those patients where we know the benefit really does outweigh the risk.

DR. BURMAN: Thank you.

Dr. Thomas?

DR. THOMAS: Just wanted to reiterate the

issue about the contraception because it's multi-factorial. One is the effect on oral contraceptives, which clearly has to be in the labeling and emphasized. And the second point is because of the issues of attention and memory, you're taking a group that may have an ineffective oral contraceptive and they may forget to take it.

Other methods of contraception, such as barrier, you also have to remember to use it properly and to use it as well. And disruptions in concentration or memory may impact the proper use of barrier methods as well. So you have multiple methods that, even if you're using more than one, may fail because of the medication side effects.

DR. BURMAN: Yes, please, Dr. Colman.

DR. COLMAN: Yes. I wanted to ask Dr. Heckbert, in response to your comment about you'd like to see more data before the drug were approved, do you have any specifics on what kind of data?

DR. HECKBERT: Well, Dr. Cragan mentioned that there might be data that we don't even have now that I'm wondering whether that might be forthcoming

soon on topiramate-exposed women from, I guess, antiepileptic or migraine indication. I don't know. So if there are more data out there somewhere, that would be great.

But we heard about a 10,000 person study. That might really result in five times as many pregnancies if the ability to prevent pregnancies is similar to what we had in the existing data. So I think that would be added here somewhere. But 100 to 125 pregnancies, that kind of number is half of what's in this North American AED registry study. It would take a lot of people. But that's going to be the kinds of numbers you'll need for a cardiovascular safety study also.

DR. BURMAN: Thank you. And although this discussion is focusing on the committee, I think if there's a point of clarification that the sponsor would like quickly, that would be fine.

DR. GADDE: Thank you. Actually, I won't talk as a sponsor representative. I just thought I'll add some information that can help you.

I believe I agree with everyone that talked

here. We don't know. And if the rate of risk is 2, it's still 2. It could be lower. And that's true for most drugs on the market. The drug is on the market for two indications, and some of our colleagues here are using it in women who become pregnant.

I strongly suggest to the sponsor, in the registry that will go forward, as important is that the control group won't be women with epilepsy. They should be women who have obesity, matched for the same level of obesity. That will be the careful way to do the job.

We can do it. Thirty percent of our patients are obese. They call Motherisk. They call other teratogenic centers. So we can -- and if a signal come up, it will come up very clear because the numbers will be as the colleagues here said. So I think a careful and well-designed registry is the only way to do it right, with the appropriate controls.

DR. BURMAN: Thank you.

Dr. Proschan?

DR. PROSCHAN: Yes. I think the registry idea, I think, is a good one because in a clinical

trial, as opposed to a registry, as soon as they get pregnant, you're going to tell them, go off this drug. And that probably doesn't happen in the real world. So that would be more real world-like, I think.

DR. BURMAN: Dr. Rogawski?

DR. ROGAWSKI: Yes. I just wanted to state what may be obvious, but maybe not. And that is that these teratogenicity studies are extremely difficult to do. They take a long period of time, and there's no way that they can be done premarketing. They have to be done in a postmarketing fashion when large numbers of women are exposed. So I just wanted to emphasize that fact, that this wouldn't necessarily be a reason not to approve the drug.

DR. BURMAN: Thank you.

Yes, please.

DR. HENDRICKS: We shouldn't forget, though, that phentermine has been around for a long time, and so has topiramate. And so there's already -- unless you're proposing that there's some synergy between the two drugs, there's no reason to suspect that there is. And so we already have a fair amount of data. I don't

think we should not approve the drug because we already have a fair amount of data; then we should go ahead with it.

DR. BURMAN: Thank you.

Dr. Colman, you had a comment?

DR. COLMAN: Yes. I just want to remind people that Dr. Roberts presented the data from the abstract from the teratology meeting. It wasn't formally put up there, but for isolated cleft, the odds ratio was more like 10. So we're far above the 2, 3 range. It's limited data, sure, but that's an odds ratio that you don't generally ignore.

DR. BURMAN: Yes, Dr. Morrato?

DR. MORRATO: I'd like to see what that study is. It sounded like you only had the abstract in terms of information, so it is a starting point. Maybe others know about it. But it would be good to see the actual detail.

DR. ROBERTS: The abstract was just last month at a meeting, and I guarantee you there's a manuscript that's in preparation.

DR. MORRATO: But in terms of having to

start from scratch with a brand-new study, which is, I think, what I heard you mentioning, at minimum you'd want to see that information in detail.

DR. BURMAN: If we might --

DR. GADDE: Again, if I can give you the information. The sponsors of this study will refuse to release any information before end of 600. So I think anything we do now is in our interpretation. No other registry found more cleft lip.

So while I appreciate showing it, you have to look at everything together. And Lou Aronne and the team say that an N of 600 is needed for each drug to get to their power. So you are not likely to see more.

DR. BURMAN: Thank you.

Dr. Bersot?

DR. BERSOT: Back to the issue of the effects of topiramate on birth control pills. Apparently doses of topiramate up to 200 milligrams a day don't significantly affect, in PK studies, area under the curve for ethinyl estradiol or norethindrone. So I'm not sure that the doses that

are going to be used in Qnexa are going to have any effect on the efficacy of oral contraceptives.

DR. BURMAN: Thank you. Nice discussion. Thank you for the discussion, and also for the sponsor for clarification.

Does anyone have any further questions or comments?

[No response.]

DR. BURMAN: Then again, let me try to summarize, with your help.

With regard to teratogenicity, different studies have come out with somewhat different rates of relative risk of teratogenicity. And of course, they're using higher doses of medication. It may be as much as two- to threefold increase. And in one study, the risk of cleft palate was increased significantly to tenfold, but as was pointed out, this isn't consistent in all the studies.

We're concerned about the large number of patients that might be exposed to the medication who would have inadvertent pregnancies. The risk, however, to teratogenicity seems relatively low.

We're concerned about the risk of teratogenicity even in obese patients. And that has to be used a control in a registry that will also include issues such as weight loss. The control group, as I mentioned, is an issue, and it should be obese patients.

Antiepileptic drugs, usually in higher doses than used here, are known to be teratogenic, and there's a question whether dose relation is important for teratogenicity or whether these are idiosyncratic. We're concerned about the breast lactation study and what information that might give, and also about ensuring that there is a closely controlled registry.

So with that information, we'd like now to move to the voting question, which is up on the board. The question is, of course, the important one.

Based on the current available data, do you believe the overall benefit/risk assessment of Qnexa is favorable to support its approval for the treatment of obesity in individuals with a BMI greater than 30 kilogram per meter squared, or greater than or equal to 30 kilogram per meter squared, or greater than or

equal to 27 kilogram per meter squared, with weight-related comorbidities?

We will vote, and then we would like to go around to each individual for individual discussion. We will be using an electronic voting system for this meeting. Each voting member has three voting buttons on your microphone, yes, no, or abstain.

Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. I will read the vote from the screen into the record.

Next we will go around the room and ask each individual who voted to state their name and vote into the record, as well as the reason why they voted as they did.

Is there any quick discussion -- excuse me -- before we vote? Dr. Kaul?

DR. KAUL: Yes. I would like the FDA to clarify, what do they mean by weight-related comorbidities? I mean, is it risk factors, or with

established serious heart disease, vascular disease, for which we have zero information?

DR. COLMAN: Yes. That's just kind of a carryover from years of -- this is kind of standard language. So BMI of 27 or higher with hypertension, dyslipidemia, type 2 diabetes.

DR. KAUL: But not ischemic heart disease, cardiovascular disease, established cardiovascular disease?

DR. COLMAN: We haven't gotten that far.

DR. KAUL: So then we will have to use a restricted definition of this, then.

DR. COLMAN: Yes. I guess, for simplicity, let's stick to hypertension, diabetes, dyslipidemia.

DR. KAUL: Okay. That's helpful.

DR. BURMAN: Thank you.

Anybody have any other clarifying questions?

[No response.]

DR. BURMAN: Then what we will do is go ahead and vote, if everyone's ready. So vote yes, no, or abstain.

DR. TRAN: And for those of you who are not

familiar with this, it will continue to flash, even if you pushed your choice already. If you're unsure, you can push it again, up to four times. It's a carryover from yesterday.

[Vote taken.]

DR. BURMAN: Everyone ready?

So the results are 7 yes, 9 no, and zero abstain. And I think we'll read into the record.

Those who voted yes are Dr. Capuzzi, Dr. Bersot -- I'm sorry. Voting yes were Dr. Capuzzi, Ms. Coffin, Dr. Goldfine, Dr. Henderson, Dr. Hendricks, and Dr. Rogawski. Voting no -- and Dr. Kaul as well saying yes. Thank you.

No include Dr. Bersot, Burman, Cragan, Flegal, Heckbert, Morrato, Proschan, Thomas, and Weide. And we'd like to go around the room, perhaps starting with Dr. Rogawski, to give your rationale for your vote and to address the issues mentioned.

DR. ROGAWSKI: Thank you, Mr. Chairman. Well, clearly we need more information about this medication. But I think that the type of medication we need, particularly with respect to teratogenicity,

can't be gained in a clinical trial setting. It can only be gained once the drug is on the market and large numbers of individuals are exposed to it.

So I think that in terms of balancing the risks and the benefits here, I came to my conclusion to vote in favor of approval because it's clear that these two components, as well as the combination, are indeed going to be used by patients because they are available.

It seems to me that the best use by patients would occur with the most information and with the proper labeling, the proper education, and so forth, as would be done if the sponsor was marketing the drug and presenting the drug combination to the public.

So I think, overall, there's a greater concern with respect to public safety if we have non-approval because that means that we don't have the benefit of the additional information and education, risk mitigation strategies, and so forth, being presented to the public. So that's the reason why I voted in favor of approval.

Oh, one other point I wanted to make.

Dr. Roberts leaned over at the end of our question with respect to the bicarbonate reduction and asked about whether if your summary comments you had included the concern with respect to children and also with respect to adolescents that we heard the committee comment on. And so, hopefully, that will be reflected in the record.

DR. BURMAN: Thank you for pointing that out.

DR. MORRATO: Elaine Morrato, and I voted no. And actually, many of my reasons are very similar to what you just shared. I just erred on the no side in terms of until risk management.

So I definitely agree that there's a significant obesity epidemic in the United States, and therefore the public health and medical need is great for effective and safe pharmacotherapy options to be approved. I also agree that the Qnexa was shown to be quite effective, and that the FDA's guidelines for weight loss, it needs to be remembered, was in the context of a very proactive lifestyle modification and diet.

But my concerns were the public health consequences, given the long list of safety risks that were listed for the drug, and the strong pent-up market demand for effective weight loss pharmacotherapy. That is, the drug will be used by millions of patients over long periods of time, far exceeding the label indications for use and duration of clinical experience that we have.

As Dr. Weide said, it's chronic disease requiring chronic treatment. And while it's always challenging when individual patients have personal success stories, I had to ask myself, to balance against the initiating a huge public health experiment, as was mentioned by Ms. McAfee during the public health hearings.

So I erred on no. However, I think there's the opportunity to pay more careful attention to the REMS in particular. And in addition to the registry trials and gathering more data, which I agree are very important, I think there could be more careful attention to a staged launch, perhaps.

There was no discussion, really, as to how

the marketing would progress, if it would be very open to a broad public, in primary care as well specialists. I'm wondering whether or not in a staged launch we could be more careful about how it gets out in the market in terms of specialists, weight loss clinics, et cetera, where we know that those patients are more likely to meet the indicated use that they were seeking.

The other piece, I think that if it is to be approved, we need better, earlier assessment of knowledge, attitudes, and behaviors much earlier than 18 months. I would recommend that we actually couple quarterly, understanding, if you will, the same way companies track market share and prescriptions.

If you have those lists of doctors, you can also be tracking knowledge and behavior over time to make sure if there's early intervention that needs to happen, you have the opportunity to do that.

I agree also with the maternal health team's recommendations. If it is to be approved, it would be a category X, and that there be attention made to really think through the development and pretesting of

the medication.

I know at this point if there is an approvable letter, it's very easy to say, let's quick get some research together. But I'm fearful that the time and attention to really develop it in a way that's going to be effective would get shortcut.

So I'd want to make sure that it really is quantitatively tested in all of the risk groups, including special subpopulations, men, women, elderly, and racial and ethnic subgroups.

DR. HENDERSON: I'm Jessica Henderson, and I voted yes for approval. I did vacillate between yes and no because of the lack of long-term safety data and also the real world applications that we all discuss we're worried about.

But I voted yes because, number one, the sponsor did satisfy the criteria for the weight loss benchmarks. But mostly what made me vote yes is the quality of life survey data. Five out of the eight quality of life measurements were statistically significant in improvement.

As the consumer representative, I put a lot

of credence into quality of life and the pursuit of life, liberty, and happiness, and a patient's right to do that. So the quality of life data actually put me in the yes category.

DR. GOLDFINE: Allison Goldfine, and I voted yes. And I've been on many committees, and I've never found a vote actually harder. And I think that in the comments, you're going to hear that the panel was probably closer despite the split vote.

I also thought there should be a controlled and staged launch. I would like to see that the outcome trials and longer-term are actually initiated, certainly coincident with approval of the drug. I would like to see the review of the two-year data before the approval of the drug.

I would like to restrict patients initially who have established coronary artery disease, and potentially other very high risk individuals; certainly elderly, certainly the cautions in youth that have been discussed.

Of all the things that concerned me most was the pregnancy issue, and that to me was very

problematic because I don't want a real world trial where the vulnerable are not the ones who agreed to the risk exposure that was enforced upon them. And yet I also clearly agreed that you would not be able to get this data from a clinical trial design, and I think that's what finally swayed me.

Therefore, the risk management program and the registries and the careful assessment that these are established before the approval, and that the mechanisms are in place, are going to be essential to support the vote that I was on the fence because of all of these lists of restrictions, and in addition some of the others that had been discussed, including Holter monitoring, bone mineral density, and others that were not as major as the pregnancy and depression issues.

DR. PROSCHAN: I'm Mike Proschan. I voted no. I also had a very difficult time. Part of my reasons was that a lot of these potential problems are sort of brain-related, depression, anxiety, memory, cognitive. And that always makes me worry a little more than with other kinds of problems, although I

think there were other problems that certainly were brought up that I don't think we have enough data to really be able to say whether they are serious issues or not.

I think if we had had longer follow-up, I probably would have voted the other way. But I just don't feel comfortable with one year follow-up. In clinical trials, people often say, well, how do you know that it won't cause cancer in 15 years? The answer is, we don't know. We do five-year trials. We don't know whether it might cause cancer in 15.

But when you only do a one-year trial, to me I'm not willing to make that leap that in another year, there might not be problems that revealed that these are very serious and they don't go away.

DR. BURMAN: Thank you. Ken Burman. I voted no, but it's a no with a lot of explanations. And I agree that the committee seems to be closer than perhaps appears.

That I think my no vote will allow further discussion, with the thought that it would allow further discussion with the FDA to address some of

these issues, I wouldn't be upset if it were approved with a lot of explanation, as we mentioned.

As we know, obesity is a major health problem, and all efforts to address this issue should be lauded. Qnexa does meet or exceed the agency's requirement for efficacy; I don't think there's any issue there. The related topic, though, of course, is that the patients will lose a percentage of weight, 6 to 10 percent, perhaps, and still may not reach their goal weight, but this will be helpful, especially in a longer term program.

On the other hand, the medication has serious potential adverse effects, including potential teratogenicity, increased suicidal ideation, cognitive issues, decreased bicarb, tachycardia, and possible renal stones. Some of these side effects are serious and could be life-threatening, and they have to be weighed against the potential of a relatively modest weight loss and its long-term health benefits.

It is difficult if not impossible to weigh these issues since the clinical studies are only for about a year and these medications, if approved, will

be used for a much longer time frame in a much wider population. And it is difficult to extrapolate the potential adverse effects to this larger population.

The doses of medication presently approved on the market are not identical to the doses in these medications, so it's difficult to extrapolate from other studies using the medication when it's used for seizures.

My recommendations agree with the FDA recommendations, that if the medication is approved, it should be tightly regulated. I agree with their specific recommendations for designating it category X, having a REMS program with details, a registry that is specific and detailed, and performing a prospective observational cohort study.

I don't have strong views regarding the lactation protocol. The question remains open in my mind whether it is worthwhile to approve a medication for moderate weight loss when it has significant potential issues.

However, I could have voted yes, and will feel more assuaged if a lot of these issues and

restrictions were addressed, especially with regard to warnings for specific populations, as mentioned. Thank you.

DR. FLEGAL: Katherine Flegal. I also voted no. I had a lot of different considerations here. I do think this drug fills a very important niche, as the sponsor pointed out, and it's quite effective.

I think my views -- I think it was both colored, maybe, by our experience with Avandia and the safety concerns that we should deal with them before rather than afterwards.

As Lynn McAfee said, this is like a public health experiment, a large gamble. And I think widespread usage even in inappropriate populations is difficult to prevent. We have one-year information, but this drug will likely be used for a long time. It really addresses surrogate endpoints, and there's minimal information on subgroups, even, like sex and ethnic groups.

I think we need more data. I would like to see more data on body composition because there's -- I'm thinking about the health effects have more to do

with body composition aspects than simply BMI alone.

The use of this drug would not in itself get rid of obesity. I don't think we really know if it would either improve health or save money on a population basis. And I think that the risk management is a very difficult challenge, and that we need more information and research on how to really monitor this, how to control access.

DR. THOMAS: Abraham Thomas. I voted no. And just to preface, before I moved to Henry Ford, for six years I was the medical director of a weight management program at the Brigham, taking care of thousands of patients with obesity.

The current medications available are not very effective and have a lot of side effects. The sponsors did an outstanding job of proving the efficacy, and this medication in terms of efficacy is far superior to anything that's on the market.

The concerns we have are with safety. And as previously mentioned, we want to make sure we don't avoid a situation where, five years from now, we're back from an advisory meeting considering safety

issues.

So there's a few things that I think have to be addressed, and I think it's best that these are addressed before approval, or at least started before approval so that they can be finished soon after the medication is released.

The first is cardiovascular disease. Most of us who treat obesity, when we use phentermine, use fairly precise criteria about which patients we shouldn't give them to. We don't give them to people who have a history of an MI. We don't give them to people who have other atherosclerotic disease, such as a stroke.

Potentially, patients could get that. As part of a trial, you'd have to use high risk patients if you want to be able to do the trial within a time span that's reasonable. Many of the patients in this study had high CRP levels, but that's not unexpected, because women who are obese will have high CRP levels. But if you were to look at their Framingham risk scores, they probably are quite low, and their gen-year risk of an event is very low.

The MIs that did occur were all in the treatment group and were all in individuals -- the youngest one was in their mid-50s, but in the 60s, and two of them are men, in spite of the fact that men a very low proportion of representation in this study.

So I think we should start a cardiovascular trial to look at outcomes in a higher risk population before release so we have the data within two to three years of release of the medication.

The second thing is I'm very concerned about bone health. We were really surprised about bone health. The TZDs were a surprise, and then we were getting surprised that type 2 is a risk factor, potentially, for bone disease.

This medication, because of the acidosis, could affect both spectrums of bone health, peak bone mass in the younger generation -- because peak bone mass is developed through the mid-20s -- and then osteoporosis or fracture risk in the older subjects.

I think this data could be accumulated as part of some of these studies that are done for safety because they'll have large numbers to tell, and

hopefully we'll also have fracture data from the sponsor at a later point.

The third thing is the sponsor used a restricted fat diet, not a low carbohydrate diet. Most patients, when they're going to use this, will pick a diet of their own, in spite of what we tell them. So we do need to have some real world data of what happens when people are on a low fat diet versus a high fat diet. A ketogenic diet that's high fat, like the Atkins diet, may contribute to more issues of acidosis than the high carbohydrate diet. So I think some data on that would be important to know what happens with acidosis.

We do need more information about suicide risk. It took 10- or 12,000 patients for rimonabant to have that signal to be really clear. The meta-analysis also needed a lot of patients with topiramate. So I think as the course of data is being obtained for these other outcomes, like cardiovascular disease, that data can also be obtained in terms of depression and suicidal ideation.

Then finally, I think we have to get away

from the concept of usage for a short term. Obesity is a chronic disease. Blood pressure is a chronic disease. I would never go to someone who has high blood pressure and say, your blood pressure is normal; now we stop all your medications; see you in a year. But with obesity, we view it that way. So we have to look at the long-term safety of these medications so we can prevent weight regain.

DR. BERSOT: I'm the second of the doubting Thomases. Pretty much what's been said are the reasons why I voted no. I realize that without a registry, the issue with regard to pregnancy can't be resolved. A staged launch is a good idea, but in the real world I don't how you really are going to be able to do that.

We need more evidence in the high risk cardiovascular disease patient. And then there are two elephants in the room that no one has mentioned today, and those are lorcaserin and the other drug that's on its way to this committee that have probably not as great efficacy in terms of weight loss, but may be better risk factor profiles. But we don't know

that, and I would like to know more about all of these three different compounds before making a decision about any particular one.

DR. WEIDE: Lamont Weide. Can we have three doubting Thomases in a row? I voted no, and really, I'm glad to see -- and it doesn't surprise me among people who are treating people with obesity that we're starting to call it a chronic disease. I'm delighted to be quoted, thank you, but you have to think that way. And I think when you think that way, then you look at the drugs differently. And you have to say, tell me what's going to happen with my patients as I allow them to stay on the medication. And that's one of the things that bothers me.

If, with a year's trial, you have double the depression risk and you have some cardiovascular questions, I would like to see it extended. I would like to see the at-risk population be sicker, if you will, so that we can find out whether or not these safety concerns are going to be a major issue.

I would agree, I am really sick of taking medicines off of the market after they've been on a

year or two because we've identified something that we didn't know about. And that really is some of what has given the FDA a reputation outside in the public.

I would say that as I've joined the committee, my respect for the FDA has markedly increased. I think everybody is trying to do their best job. But we do have a responsibility to protect the public at large, and that means, although as much as I feel for the people who want this drug and want to lose weight, we have to protect the population at large. And I think we just need longer term data with the people who are really going to be using it out there rather than a select group of patients in fairly good health.

DR. CAPUZZI: Yes. I voted yes, but I actually made a mistake. I have to be very frank. This is my third meeting, and as Dr. Burman was jotting everything down and all the various concerns, my yes was predicated on the fact that these would all be met first. But I made a mistake, so it's really no at this point.

DR. KAUL: Kaul. I voted yes. There's a

very fine line between a yes and a no vote, and thankfully, the FDA pays more attention to the discussion rather than just counting the beans. My yes vote comes with a lot of conditions. And I will not hold it against the sponsor if they interpret my yes vote as a no vote.

First of all, it should only be approved for low to medium dose, not for the high dose, because all the safety signals appear to cluster in the high dose. The sponsor should be required to conduct a pharmacodynamic study in the short term addressing the concerns that were expressed earlier on during the discussion, focusing specifically on commonly used medications, including cardiovascular and over-the-counter medications.

There should be a clinical outcome study designed to rule our cardiovascular risk. It should be implemented within three to six months. The protocol should be with the FDA within three months. And the study outcomes should be available to the FDA for assessment within three to five years. It should be a conditional approval. If they don't meet these

conditions, the FDA should have the right to withdraw the approval.

There is already a FADAA program that sort of enforces postmarketing requirement for assessing safety signals. I have no doubts about its effectiveness. But I think it concentrates the sponsor's mind if we impose, moving forward, a preapproval requirement to evaluate cardiovascular risk. And I think the FDA should seriously consider that as an option.

It's already been mentioned what patients it should not be given to. There should be strict contraindications in patients with arrhythmic heart disease, severe ischemic heart disease, patients with hypertensive heart disease, including TI and stroke, and it should be contraindicated. And there should be a prominent warning mentioned for adverse effects, particularly the drug interactions that have already been elucidated.

So as I said, a very fine line between a yes and a no vote.

DR. HENDRICKS: Ed Hendricks. I voted yes.

I agree that the population at large needs to be protected from dangerous drugs; however, one-third of that population is already obese, and there's a very large segment of the population who are headed that way.

I think that Qnexa does meet the FDA efficacy thresholds. I think the sponsor did an outstanding job of managing several very difficult clinical trials, and did an outstanding job producing the data, and that the data does show that the safety issues in the target population, which are the obese patients, that the drug is reasonably safe and that we should approve it.

I think it does fill a gap in our treatment spectrum. I think if the drug is disapproved, we're going to send a very board message to the obese and the overweight, and that that will further drive them away from medical solutions to this problem to all the various quackery things that are out there. And so I hope the FDA doesn't go just by the beans, as we discussed.

MS. COFFIN: Hi. Melanie Coffin, and I

voted yes. And I'm a little surprised. I can agree with some of the things that have been said. Dr. Thomas, I do agree that the drugs that are available right now, they don't work very well and they've got really bad side effects, way more -- just a lot of side effects. And I do believe that the side effects that were listed here were reasonable, with a doctor's care.

I disagree with Dr. Capuzzi, who said that these folks were in really good health. I think that the sponsor did a great job including people with past mental illness, with depression, and comorbidities. And I thought that it was much more real world than some of the others studies that I've seen come through on other weight loss drugs.

I think that because these drugs stand alone, are already on the market with higher dosage, you're going to continue to run the risk of doctors prescribing them off label. And you're going to get higher instances with higher concentration, like Dr. Rogawski pointed out.

The funny stuff that's on the market that

does not go through FDA, people are clamoring for it hand over fist. And so, again, I do feel like we're letting perfect get in the way of possible. If there are 100 drugs out there for high blood pressure for doctors and patients to choose from, there should be more than half a dozen for obesity and overweight treatment.

DR. CRAGAN: I voted no, and I also found it a very difficult decision. This drug is clearly effective and has the potential to change many people's lives. And I really hate to be on record voting against that.

But in the end, I couldn't really justify widespread use with the reproductive outcomes concerns that we have. And as I listened to the panel members discuss the other adverse events, it actually raised my level of concern rather than lessening it.

I think the situation where the only way we're going to resolve the reproductive risks, if we can, is to have a large number of women take the drugs and see what happens, is the situation we're in with human teratogenicity, often. And that's really

difficult, but that's just the nature of the situation.

DR. HECKBERT: Susan Heckbert, and I voted no. In the open public hearing, we heard from several people that obesity is a very difficult disease to combat, and that's why people are clamoring for medications. But because obesity is very difficult to combat, the medications that are used to treat it are often very strong medications with a variety of different effects.

We've talked here about how these two medications interfere with a number of different biological pathways. And as such, it's very highly effective; that was clearly demonstrated by the sponsor, highly effective in achieving weight loss. But at the same time, we have a number of signals of adverse effects that really can't be ignored that need more exploration. And the ones I'm most concerned about are the suicidality risk, the potential for cardiovascular risk based on the mechanism of action of these drugs and the heart rate signal, and of course the teratogenicity.

I do take Dr. Rogawski's point that it won't be possible to fully answer that teratogenicity question with clinical trials. But I think we do need more information about it as well as the other serious endpoints that I mentioned.

DR. BURMAN: Thank you all. Does the FDA have any -- Dr. Colman or Dr. Rosebraugh, do you have any concluding remarks?

DR. ROSEBRAUGH: Well, I'd like to thank the panel members. This has been a very helpful discussion.

I do have some concluding remarks. It doesn't have to do particularly with this AC. And it's a public acknowledgment of Ken, so I would like to take just a couple moments to do that. And believe me, after the last three days, I don't want to stay here very long, either. So I will try to make this as short and sweet as please.

On the other hand, it's come to my attention that this is your last official day. And so people come to me -- I've been doing this game for about 10 years now. I've seen a lot of chairs. In fact, I

have another AC next week, so I'm not even going to have time to regroup from this one.

So there's always a list that we go through, and we hope that people kind of -- when we get a chair, they have some of these qualities. And I have this list I keep with me.

So you want a chair that comes prepared. You want them to be dedicated to public health. They have to be able to lead under pressure, and have to have grace under pressure. They have to have a light touch while they're doing that, but there has to be a hint of being able to get firm with that touch if it's necessary.

You want somebody that has fairness. You want someone that has intellect, practicality, and can herd cats. That's a good quality to have. And then what I consider an accessory, like if I'm buying a car -- if I got some of those other things, that's okay. But an accessory is if they modesty, well, you've got everything.

So from now on, I don't really need this list. If I'm going to describe all the qualities of a

perfect chair, I'll just talk about you.

[Applause.]

DR. ROSEBRAUGH: So let me just say I personally want to thank you for your collegiality, and for making my life, Dr. Colman's, and Dr. Parks' life a lot easier. And we usually have a plaque and stuff, and so we'll get you a plaque and all that. But you're going to get my highest reward, and that's for me to say, attaboy, and thank you.

[Applause.]

DR. BURMAN: Thank you very much. That means a lot to me, an I'm very appreciative and very humbled by it. If I might, I have a short comment as well. And I really appreciate all of the interactions. As you mentioned, I'm rotating off the Advisory Committee, and I'd like to take this opportunity to make a few brief comments.

It's been a unique and gratifying experience to serve on the committee, and special privilege to serve as the chair. My interactions with the FDA have demonstrated to me that the staff is intelligent, wise, reasonable, and open-minded, whose main goal,

which they take very seriously, is to serve and protect the public.

They perform the very difficult task of reviewing and interpreting a wide range of studies, often conflicting, and then arriving at the most reasonable and appropriate decision. All meetings, but especially the recent rosiglitazone meeting, illustrates their open and transparent process, which we all believe is critical for the agency to reach a prudent decision.

They typically not only allow but encourage active discussion of conflicting views. I have nothing but kind comments regarding my interactions with individuals at the FDA, and I hold them in the highest esteem.

I'd like to acknowledge the deduction and reasonable approach by all members of the panel, who take their tasks seriously and perform it exceedingly well. It has been a pleasure to work with them.

I would also like to note my personal appreciation to Dr. Parks, Rosebraugh, Colman, and Woodcock for their affable, reasonable, intelligent

approach to all issues, and in all my interactions. Paul and Cicely have accomplished Herculean duties with grace and humility.

Each of these staff members serve, in my view, as the paradigm of a public servant. I salute them all, and wish them continued success in their endeavors to serve the public. Thank you.

[Applause.]

DR. BURMAN: With that, thank you very much. I'll take this opportunity now to adjourn the meeting.

(Whereupon, at 4:30 p.m., the meeting was adjourned.)