

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS
ADVISORY COMMITTEE

Date: March 28, 2012

Time: 8:00 am - 5:00 pm

Location: FDA White Oak Campus

White Oak Conference Center
10903 New Hampshire Avenue
Silver Spring, Maryland

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

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1 P R O C E E D I N G S

2 DR. THOMAS: Good morning. I'd first like to
3 remind everyone present to please silence your cell
4 phones, Blackberries, and other devices if you have not
5 already done so. I'd also like to identify the FDA
6 press contact, Ms. Erica Jefferson.

7 If you're here, present, please stand.

8 Good morning. Good morning. My name is
9 Abraham Thomas. I'm the chair of the Endocrinologic
10 and Metabolic Drugs Advisory Committee. I will now
11 call the meeting of the Endocrinologic and Metabolic
12 Drugs Advisory Committee to order. We will go around
13 the room and please introduce yourself. We'll start
14 with the FDA and Dr. Rosebraugh to my left and go
15 around the table.

16 DR. ROSEBRAUGH: Good morning, everyone.
17 Curt Rosebraugh, director, Office of Drug Evaluation
18 II.

19 DR. PARKS: Good morning. I'm Mary Parks,
20 division director, Division of Metabolism and
21 Endocrinology.

22 DR. COLMAN: I'm Eric Colman, the deputy

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

3

1 director for the Division of Metabolism and
2 Endocrinology.

3 DR. KAUL: Good morning. Sanjay Kaul. I'm a
4 cardiologist from Cedars-Sinai Medical Center in Los
5 Angeles.

6 DR. KRAMER: I'm Judith Kramer, associate
7 professor of medicine, Duke University.

8 DR. KONSTAM: Marv Konstam, cardiology from
9 Tufts Medical Center in Boston.

10 DR. FELNER: Eric Felner, associate professor
11 of pediatrics, division of pediatric endocrinology at
12 Emory University in Atlanta.

13 DR. WEIDE: Lamont Weide, professor of
14 medicine, chief of endocrinology, University of
15 Missouri-Kansas City and Truman Medical Centers.

16 DR. YANOVSKI: Jack Yanovski, chief of the
17 section on growth in obesity, pediatric endocrinologist
18 at the NIH intramural program.

19 DR. SPRUILL: Consumer representative Ida
20 Spruill, assistant nursing professor at the Medical
21 University of South Carolina, Charleston, South
22 Carolina.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

4

1 DR. BRITTAIN: Erica Brittain. I'm a
2 statistician at the National Institute of Allergy and
3 Infectious Diseases.

4 DR. THOMAS: Abraham Thomas, head of
5 endocrinology at Henry Ford Hospital, Detroit,
6 Michigan.

7 MR. TRAN: Paul Tran, the designated federal
8 officer for the EMDAC committee.

9 DR. SEELY: Ellen Seely, professor of
10 medicine, Harvard Medical School, and director of
11 clinical research of the endocrine division at Brigham
12 Women's Hospital.

13 MS. MCAFEE: Lynn McAfee, fat person.

14 DR. GREGG: Ed Gregg from the diabetes
15 division at CDC in Atlanta.

16 DR. GOLDFINE: Allison Goldfine, associate
17 professor, Harvard Medical School, and head of the
18 section of clinical research at the Joslin Diabetes
19 Center, Boston.

20 DR. WATERS: David Waters. I'm a
21 cardiologist from the University of California-San
22 Francisco.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

5

1 DR. BERGMAN: Richard Bergman, professor and
2 head of the Institute for Diabetes and Obesity at
3 Cedars- Sinai Medical Center, Los Angeles.

4 DR. COOPER: Bill Cooper. I'm a
5 pharmacoepidemiologist and professor of pediatrics at
6 Vanderbilt University.

7 DR. PROSCHAN: I am Michael Proschan. I'm a
8 statistician with the National Institutes of Allergy
9 and Infectious Diseases.

10 DR. HIATT: William Hiatt, professor of
11 medicine at University of Colorado School of Medicine,
12 the division of cardiology.

13 DR. JENSEN: Mike Jensen, professor of
14 medicine, endocrinology, Mayo Clinic, Rochester,
15 Minnesota.

16 DR. ALEXANDER: Hi, John Alexander. I'm an
17 associate professor of medicine and a cardiologist at
18 Duke University.

19 DR. HENDRICKS: Ed Hendricks, private
20 practice obesity medicine, Sacramento, California.

21 DR. RASMUSSEN: I'm Mads Rasmussen of Novo
22 Nordisk. I'm the industry representative.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

6

1 DR. THOMAS: Dr. Temple, if you would,
2 introduce yourself.

3 DR. TEMPLE: Bob Temple. I'm deputy center
4 director for clinical science.

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

15 In the spirit of the Federal Advisory
16 Committee Act and the Government in the Sunshine Act,
17 we ask that the advisory committee members take care
18 that their conversations about the topic at hand take
19 place in the open forum of the meeting.

20 We are aware that members of the media are
21 anxious to speak with the FDA about these proceedings.
22 However, the FDA will refrain from discussing the

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

7

1 details of this meeting with the media until its
2 conclusion. Also, the committee is reminded to please
3 refrain from discussing the meeting topic during breaks
4 or lunch. Thank you.

5 MR. TRAN: Good morning. The Food and Drug
6 Administration is convening today's meeting of the
7 Endocrinologic & Metabolic Drug Advisory Committee
8 under the authority of the Federal Advisory Committee
9 Act of 1972. With the exception of the industry
10 representative, all members and temporary voting
11 members of the committee are special government
12 employees or regular federal employees from other
13 agencies and are subject to federal conflict of
14 interest laws and regulations.

15 The following information on the status of
16 the committee's compliance with federal ethics and
17 conflict of interest laws, covered by, but not limited
18 to, those found at 18 U.S.C. Section 208 and Section
19 712 of the Federal Food, Drug, and Cosmetic Act, is
20 being provided to participants in today's meeting and
21 to the public.

22 FDA has determined that the members and

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

8

1 temporary voting members of this committee are in
2 compliance with Federal ethics and conflict of interest
3 laws. Under 18 U.S.C. Section 208, Congress has
4 authorized FDA to grant waivers to special government
5 employees and regular federal employees who have
6 potential financial conflicts when it is determined
7 that the agency's need for a particular individual's
8 services outweighs his or her potential financial
9 conflict of interest.

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

16 Related to the discussions of the meeting,
17 members and temporary voting members of this committee
18 have been screened for potential financial conflicts of
19 interest of their own, as well as those imputed to
20 them, including those of their spouses or minor
21 children and, for the purposes of 18 U.S.C., Section
22 208, their employers. These interests may include

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

9

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

4 The agenda involves the role of
5 cardiovascular assessment in the pre-approval and post-
6 approval settings for drugs and biologics developed for
7 the treatment of obesity. This is a particular matters
8 meeting during which general issues will be discussed.
9 Based on the agenda for the meeting and all financial
10 interests reported by the committee members and
11 temporary voting members, no conflict of interest
12 waivers have been issued in connection with this
13 meeting.

14 To ensure transparency, we encourage all
15 standing members and temporary voting members to
16 disclose any public statements that they have made
17 concerning the topic at issue.

18 With respect to FDA's invited industry
19 representative, we would like to disclose that Dr. Mads
20 Rasmussen is participating in this meeting as a non-
21 voting industry representative, acting on behalf of
22 regulated industry. Dr. Rasmussen's role at this

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

10

1 meeting is to represent industry in general and not any
2 particular company. Dr. Rasmussen is employed by Novo
3 Nordisk.

4 With regard to the FDA guest speakers, the
5 agency has determined that the information to be
6 provided by these speakers is essential.

7 The following interests are being made public
8 to allow the audience to objectively evaluate any
9 presentation and/or comments made by the speakers. Dr.
10 Robert Eckel has acknowledged that he is a scientific
11 advisor for Eli Lilly, Genentech, and Amylin and
12 receives less than \$3,000 per year from each firm. As
13 a guest speaker, Dr. Eckel will not participate in
14 committee deliberations, nor will he vote.

15 We would like to remind members and temporary
16 voting members that if the discussions involve any
17 other products or firms not already on the agenda for
18 which the FDA participant has a personal or imputed
19 financial interest, the participants need to exclude
20 themselves from such involvement, and their exclusion
21 will be noted for the record. FDA encourages all other
22 participants to advise the committee of any financial

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

11

1 relationships that they may have with the firm at
2 issue. Thank you.

3 DR. THOMAS: We will now proceed with the FDA
4 opening remarks from Dr. Eric Colman. I'd like to
5 remind public observers at this meeting that while this
6 meeting is open for public observation, public
7 attendees may not participate except at the specific
8 request of the panel.

9 Dr. Colman?

10 DR. COLMAN: Thank you, Abe.

11 I want to very briefly mention why we're here
12 today. In 2008, the Division of Metabolism and
13 Endocrinology Products held a two-day advisory
14 committee meeting to discuss the assessment of
15 cardiovascular safety of drugs used to treat diabetes.
16 That meeting led to the issuance of FDA's guidance for
17 evaluating cardiovascular risk in new anti-diabetic
18 therapies.

19 Given that a large proportion of patients
20 with type 2 diabetes are overweight or obese, it is not
21 surprising that this population of patients is and will
22 continue to be prescribed weight loss drugs. Since the

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

12

1 diabetes cardiovascular risk assessment guidance was
2 published, many have asked if the division planned to
3 implement similar guidance for the obesity drugs.

4 In 2010, the division reviewed several
5 applications for obesity drugs that raised questions
6 regarding cardiovascular safety, increases in blood
7 pressure, for example, and the potential need for
8 cardiovascular outcomes trials designed to show lack of
9 cardiovascular harm or perhaps cardiovascular benefit
10 with obesity drugs.

11 So for these two principal reasons, we
12 decided to convene this two-day meeting to seek input
13 from the committee on how best to assess the
14 cardiovascular safety of drugs used to treat obesity.

15 If I could, Paul, could I have the agenda?

16 MR. TRAN: Unfortunately, I did not make a
17 slide for the agenda, just the order in which they're
18 speaking.

19 DR. COLMAN: Let me just briefly run through
20 what we have on tap for today. The first presentation
21 will be by FDA. Dr. Julie Golden will provide you with
22 an overview of the 2007 draft guidance for development

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

13

1 of obesity drugs, hit the high points. And then we'll
2 have two reviewers from the Office of Surveillance and
3 Epidemiology who will provide you with some drug
4 utilization trends for anti-obesity use, as well as
5 duration of use of obesity drugs. So this will give
6 you a sense of the real-world use and pattern of use of
7 obesity drugs over the last 10 to 20 years.

8 Following that, we'll have a series of
9 presentations from guest speakers. The first will be
10 Dr. Bob Eckel, who will discuss the pathophysiology of
11 obesity and cardiovascular disease. He'll be followed
12 by Dr. Bill Knowler, who plans to speak about obesity
13 and type 2 diabetes. Following Dr. Knowler, Dr. Wing
14 will discuss the Look AHEAD trial. And finally, our
15 last guest speaker, Dr. George Bray, will discuss drugs
16 to treat obesity, cardiovascular, and other risks.

17 We then return to FDA presentations, and Dr.
18 Matt Soukup is going to discuss with you statistical
19 considerations in the design of cardiovascular safety
20 trials to rule out prespecified cardiovascular risk. I
21 daresay his is probably the most important talk, so
22 make sure you're all paying attention.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

14

1 (Laughter)

2 DR. COLMAN: I will follow Dr. Soukup, so you
3 will probably be completely confused and won't pay any
4 attention to what I say. But I will be discussing two
5 cardiovascular outcomes trials with the obesity drug,
6 rimonabant, and the obesity drug sibutramine, and
7 mainly to point out the major design features that I
8 think we can use for tomorrow's discussion when we get
9 into trial design and execution.

10 Finally, the last presentation of the day
11 will be from Dr. Jean-Mare Guettier, and he is going to
12 give you some background on the guidance for evaluating
13 cardiovascular risks for anti-diabetic medications,
14 some of the history behind that, some of what we've
15 learned since that guidance was implemented three years
16 ago.

17 So we have a very full agenda and would ask
18 that everyone try to adhere very strictly to the time
19 they've been allotted. And I'll leave it at that.

20 DR. THOMAS: Thank you, Dr. Colman.

21 Dr. Savage, would you introduce yourself for
22 the record?

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

15

1 DR. SAVAGE: I'm Peter Savage. I'm an
2 endocrinologist working at the NIDDK at the NIH. And
3 I'm involved in studies in both type 1 and type 2
4 diabetes, and was previously at the Heart Institute,
5 where I was involved with several of the large clinical
6 trials, including the ACCORD trial.

7 DR. THOMAS: Thank you. If we could have the
8 first presentation from Dr. Golden.

9 DR. GOLDEN: Good morning, everyone. My name
10 is Julie Golden. I'm a medical officer in the Division
11 of Metabolism and Endocrinology Products, and it's my
12 pleasure to provide you today with a summary of the
13 2007 draft guidance for developing products for weight
14 management.

15 So I'll start my talk by way of some
16 background, going back to 1995, which could be
17 considered to be the start of the modern era of obesity
18 drug regulation. An FDA advisory committee was
19 convened to evaluate the approval process for obesity
20 drugs and ultimately develop a guidance document. An
21 FDA official set the tone for this meeting when she
22 stated that "the biggest challenge we are hoping to

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

16

1 bring about is the approval of obesity drugs for long-
2 term use."

3 Many issues were discussed during this
4 meeting. But three major topics were, one, what should
5 be the duration and size of the phase 3 trials; two,
6 who are the appropriate patients to study and
7 ultimately be prescribed drugs to treat obesity; and,
8 three, what should be the criteria to define efficacy
9 of weight loss drugs.

10 Out of this meeting came the 1996 FDA draft
11 guidance for clinical evaluation of weight-control
12 drugs. Recommendations for duration and size of the
13 phase 3 studies included at least 1500 patients be
14 studied for one year under placebo-controlled
15 conditions to assess efficacy. For safety, it was
16 recommended that 200 to 500 of these patients continue
17 on in an open-label manner, a second year to get
18 additional safety information.

19 As for the patient population, the guidance
20 recommended that individuals with a BMI of 30 or more,
21 or 27 or more with a comorbidity, were appropriate for
22 drug therapy.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

17

1 These criteria were chosen to optimize
2 therapeutic risk benefit by targeting patients for whom
3 the expected benefits should outweigh the risks of
4 treatment with a weight loss drug.

5 In terms of efficacy, by 1995, there was
6 literature saying that as little to 5 to 10 percent
7 reduction in body weight in obese patients could bring
8 about beneficial changes, such as in glucose, blood
9 pressure, and lipids.

10 So the efficacy criteria were, mean weight
11 loss is 5 percent greater in drug versus placebo-
12 treated patients or the proportion of patients losing 5
13 percent is significantly greater in drug versus
14 placebo-treated group.

15 Since 1996, the year the guidance was
16 drafted, three obesity drugs have been approved by FDA.
17 As you can see, two of the three have subsequently been
18 removed from the U.S. market, dexfenfluramine in '97
19 for valvulopathy and sibutramine in 2010 for
20 cardiovascular harm.

21 So in 1998 and then again in 2000, NIH
22 published their clinical guidelines on the

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

18

1 identification and treatment of overweight and obesity.
2 The guidelines classified overweight and obesity by
3 BMI, as the WHO did in the mid-90s. They state that
4 weight loss medications are to be used only by patients
5 who are at increased medical risk because of their
6 weight and should not be used for cosmetic weight loss.
7 Also, they state that obesity is a chronic disorder
8 that should be treated chronically.

9 In 2004, FDA reconvened an advisory committee
10 to refine the draft guidance. FDA asked the committee
11 about the size and duration of the trials. Most of the
12 committee members felt that the size of phase 3 trials
13 should be driven by safety, not efficacy.

14 There was continued support for the one-year
15 placebo-controlled trial to show efficacy. There was
16 less support for continuing a second year, open label,
17 for safety. The majority of the committee members did
18 not support lowering the BMI criteria to include
19 individuals with BMIs down to 25, citing a lack of
20 data. They discuss that the lower the BMI and baseline
21 risk, the higher the bar for safety should be. In
22 terms of efficacy, the committee continued to support

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

19

1 the 5 percent criteria.

2 Out of that meeting came the current draft
3 guidance. So with that background, let me turn to the
4 current guidance.

5 Its purpose is to provide recommendations
6 regarding the development of drug products intended to
7 be used for medical weight loss. The guidance defines
8 medical weight loss as a long-term reduction in fat
9 mass with the goal of reduced morbidity and mortality.
10 Biomarkers such as blood pressure, lipids, and
11 hemoglobin A1c in general should demonstrate
12 improvement commensurate with the degree of weight
13 loss.

14 So as we discussed, in overweight and obese
15 individuals, particularly those with comorbid
16 conditions, 5 percent weight loss is generally
17 considered to be associated with improvement in various
18 metabolic and cardiovascular risk factors. Some
19 observational studies suggest that modest degrees of
20 intentional weight loss by diet and exercise may reduce
21 the incidence of obesity- related morbidity and
22 mortality. Despite these encouraging data, our current

1 understanding of drug- related improvements and
2 outcomes is limited and mixed. You will be hearing
3 later in the day about the SCOUT trial, in which the
4 use of sibutramine was associated with cardiovascular
5 harm.

6 In terms of the indications for obesity
7 drugs, the guidance does not make a distinction between
8 weight loss and weight maintenance. Since obesity is a
9 chronic disease, and these drugs need to be taken
10 chronically, we assume that once an obesity drug is
11 stopped, weight will likely be regained. Therefore,
12 the efficacy endpoint, that is, change in body weight,
13 must be demonstrated at one year to be statistically
14 and clinically greater than placebo, regardless of the
15 trajectory of weight loss.

16 With respect to lifestyle modification, FDA's
17 position aligns with the NIH guidelines. Dietary
18 intake, exercise, and other behaviors are considered
19 the cornerstone of obesity management. The guidance
20 states that because all drug therapies pose some risk
21 for adverse events, weight loss drugs should only be
22 considered after a sufficient trial of lifestyle

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

21

1 modification has failed and when the benefits of weight
2 loss are expected to outweigh the risks of treatment.

3 In general, the treatment effect should be
4 demonstrated on a background of realistic or real-world
5 diet and exercise. So lifestyle modifications should
6 be designed to be applicable to the use of the product
7 post- approval.

8 FDA kept the general BMI criteria in the 2007
9 guidance the same as in the original guidance and
10 consistent with the recommendation in the NIH
11 guidelines. Examples of obesity-related comorbidities
12 include diabetes, hypertension, dyslipidemia, sleep
13 apnea, and cardiovascular disease.

14 The guidance states that efforts should be
15 made to include in the studies a representative sample
16 of patients from the various demographic, ethnic, and
17 racial groups in which prevalence of obesity is
18 highest. Development programs also should include a
19 representative sample of patients with BMI greater than
20 40.

21 Just a few comments about phases 1 and 2.
22 The guidance says that before initiating phase 3

1 clinical trials, the pharmacokinetics and dose-response
2 profiles of a new obesity drug should be well-
3 characterized. The pharmacokinetic profile should be
4 examined in patients with a broad range of BMIs, as PK
5 can vary by weight or body adiposity. Early-phase
6 clinical trials should include a range of doses and be
7 designed to define the dose-response relationship for
8 change in body weight and to identify no-effect and
9 maximally-tolerated doses.

10 The duration of the phase 2 trials should be
11 sufficient to capture the maximal or near-maximal
12 weight loss effects of the active doses. Forethought
13 should be given to whether the product will ultimately
14 be used in a fixed dose or dose-titration scheme, as
15 this dosing decision will also influence the size and
16 duration of the studies.

17 Currently, phase 3 trials in obesity drug
18 development programs are placebo-controlled. As
19 discussed before, the number of patients required to
20 demonstrate weight loss efficacy will be smaller than
21 the number needed to adequately assess safety.

22 The recommendation in the guidance is for

1 3,000 patients on active and 1500 on placebo, to be
2 randomized for one year. This provides 80 percent
3 power to rule out with 95 percent confidence a 50
4 percent increase in the incidence of a particular
5 adverse event of interest when the incidence in placebo
6 is 3 percent. This sample size also should allow for
7 efficacy and safety analyses to be conducted within
8 certain subgroups, such as sex, race, and baseline BMI.

9 This figure illustrates why a drug should be
10 studied in phase 3 beyond the achievement of maximal
11 weight loss. This was a placebo-controlled, randomized
12 trial evaluating fluoxetine for weight loss. The drug
13 looked promising at week 20, but by week 52, there was
14 no difference between treatment groups. So for a
15 chronic medical therapy, we are looking for a durable
16 response.

17 The mean efficacy benchmark remains the same
18 in this guidance as in the 1996 guidance. However, a
19 new categorical efficacy benchmark was added so that we
20 weren't just looking at statistical significance, but
21 what could be considered clinically meaningful.

22 It states, "The proportion of subjects who

1 lose greater than or equal to 5 percent of baseline
2 body weight in the active product group should be at
3 least 35 percent, approximately double the proportion
4 in the placebo-treated group, and the difference
5 between groups should be statistically significant."

6 You may wonder how FDA came up with these
7 numbers. Essentially, this was done by looking at the
8 efficacy of currently approved weight loss drugs. As
9 you can see in the Xenical example, the mean placebo-
10 subtracted weight loss of 3 percent does not meet the 5
11 percent mean weight loss criterion. However, the 5
12 percent categorical analyses in the various trials
13 demonstrated statistical significance. Four out of 5
14 trials demonstrated approximate doubling of placebo.

15 We looked at this fourth study in particular.
16 It was a primary care study, so it's reflective of
17 real- world, background lifestyle intervention. The
18 results from that trial informed the proportion of
19 responders in the drug group.

20 In order to address the high rates of
21 premature patient withdrawal that are typically seen in
22 long-term weight loss studies, FDA has considered some

1 ways to handle dropouts statistically. The guidance
2 states that the primary analysis should be conducted in
3 those subjects who received at least one dose of study
4 drug and have at least one post-baseline assessment of
5 body weight. The analysis should be applied to the
6 last observation carried forward on treatment.
7 Sensitivity analyses employing other imputation
8 strategies should assess the effective dropouts on the
9 results.

10 We encourage sponsors to obtain body weight
11 measurements in all subjects who prematurely withdraw
12 from phase 3 trials near the calendar date at which
13 they were scheduled to complete the trial. For
14 example, subjects who withdraw from a 12-month study
15 after six months of treatment would come back to have
16 their body weight measured at the time they would have
17 completed 12 months of study participation.

18 Now, here is a list of secondary endpoints
19 that FDA asks sponsors to consider. Improvements in
20 these endpoints are expected after weight loss, and
21 therefore the direction of changes as compared to
22 placebo is taken into consideration when assessing the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

26

1 benefit risk of a particular medication. Obviously,
2 depending on the mechanism of action of a drug and the
3 directions seen in the clinical trials, some of these
4 can be safety endpoints as well.

5 Just a few comments on safety issues that can
6 arise with obesity drugs and have been addressed in the
7 guidance. First, body composition measurements using
8 DEXA, for example, should be measured in a subset of
9 patients at some point in development to ensure weight
10 loss is primarily fat, other than lean body mass.

11 Second, echocardiography assessment may be
12 required for certain 5-HT₂ receptor agonists. And
13 third, a comprehensive neuropsychiatric evaluation,
14 including suicidality and abuse liability, are required
15 of all centrally-acting drugs.

16 The guidance has also addressed the issue of
17 fixed-dose combinations of obesity drugs. Non-clinical
18 and clinical drug-drug interaction studies are
19 important in the evaluation. In phase 2, the efficacy
20 and safety of the combinations should be compared to
21 those of the individual components. In phase 3, the
22 combination can be evaluated against placebo in year-

1 long trials.

2 In addition to fixed-dose combinations of
3 weight loss drugs, we've also seen weight loss drugs
4 being studied to treat medication-associated weight
5 gain. Early in the evaluation of these combinations,
6 patients should have a documented increase in body
7 weight, and the efficacy and safety of the medication
8 causing the weight gain should not adversely affect the
9 weight loss drug, and vice versa.

10 So in summary, the main features of phase 3
11 programs for obesity drugs, as outlined in the
12 guidance, are as follows:

13 The program should plan for approximately
14 3,000 patients randomized to active doses and 1500
15 randomized to placebo in studies of one year in
16 duration.

17 Patients studied should be obese or have a
18 BMI of at least 27 and one or more co-morbidities.

19 The efficacy benchmark is 5 percent and can
20 be achieved by demonstrating statistical and clinical
21 significance using either a mean and/or a categorical
22 analysis.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

28

1 Finally, this slide illustrates a sample
2 phase 3 program that is representative of what we have
3 seen in the years since the draft 2000 guidance was
4 published. In this particular program, a little more
5 than half of patients completed one year of treatment.
6 That's very typical. Mean age is around 45 and the
7 majority of patients are white and female, although we
8 are starting to see more ethnic and racial diversity in
9 phase 3 programs than we had seen in the past. Mean
10 BMI is in the obese range. The majority of patients
11 had at least one weight-related comorbidity, but the
12 number of patients with previous MI was quite low.

13 So thank you for your attention. And now,
14 Drs. Borders-Hemphill and Hampp from the Office of
15 Surveillance and Epidemiology will follow with a
16 discussion of use data for drugs to treat obesity.

17 DR. THOMAS: While Dr. Borders-Hemphill is
18 making her way to the podium, Dr. Capuzzi, could you
19 introduce yourself for the record?

20 DR. CAPUZZI: Yes. David Capuzzi, Thomas
21 Jefferson University, Philadelphia.

22 DR. BORDERS-HEMPHILL: Good morning. My name

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

29

1 is

2 Vicky Borders-Hemphill, and I will present an
3 analysis of drug utilization trends on anti-obesity
4 products in the outpatient setting. The outline of my
5 presentation is as follows:

6 First, I will present outpatient prescription
7 utilization trends of anti-obesity drug products from
8 year 1991 to 2011, as well as describe dispensed
9 prescription analysis by payment methods and prescriber
10 specialty. Then I will describe anti-obesity product
11 use in patients according to body mass index as
12 reported by office-based physicians.

13 Utilization of anti-obesity drug products by
14 patient demographics of age and gender will be
15 presented for years 2008 to 2011, cumulative.
16 Concurrency analyses to assess comorbid conditions
17 using two different methods, concurrent drugs by
18 overlapping day's supply for dispense anti-obesity
19 prescriptions and concurrent diagnosis using ICD-9
20 codes, will be presented for years 2008 to 2011,
21 cumulative.

22 Finally, I will present limitations of these

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30

1 analyses and conclude with a summary of my
2 presentation.

3 The data source used for outpatient retail
4 prescription analyses was the IMS Health Vector One
5 national database. Vector One is a projected
6 healthcare database that provides the number of
7 prescriptions dispensed by retail pharmacies in the
8 U.S.

9 This data source integrates prescription
10 activity from a monthly sample received from payers,
11 including commercial plans, Medicare Part D plans,
12 cash, and Medicaid claims, as well as from switches and
13 other software systems at various points in the
14 prescription sales cycle. Data are captured from
15 nearly all of the 50,000 U.S. retail pharmacies and
16 represents nearly two-thirds of all prescription
17 volume in the U.S.

18 I will begin with the outpatient anti-obesity
19 prescription utilization. This figure shows the
20 prevalence rates of dispensed prescriptions per 100,000
21 population annually. The number of dispensed
22 prescriptions from U.S. retail pharmacies were adjusted

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

31

1 for U.S. population to account for growth from year
2 1991 to year 2011.

3 The total market of anti-obesity
4 prescriptions, represented by the blue bars, fluctuated
5 with an overall peak occurring during years 1996 and
6 1997. During this entire time period, phentermine had
7 the market lead for the number of anti-obesity
8 prescriptions dispensed, although various products have
9 come to market.

10 Public health advisories for fenfluramine and
11 dexfenfluramine in 1997, status changes for over-the-
12 counter switches in 2007 for orlistat, and sibutramine
13 withdraw from the market decreased the utilization of
14 these prescription products and contributed to the
15 fluctuating market over time. Older anti-obesity
16 medications such as phendimetrazine, diethylpropion,
17 benzphetamine continued to be prescribed throughout
18 this time period and certainly at much lower volume
19 than phentermine.

20 This figure shows the total number of
21 patients, in thousands, receiving a dispensed
22 prescription for an anti-obesity agent from the

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

32

1 outpatient retail pharmacy settings from years 2002
2 through 2011. Over 2.7 million patients received a
3 prescription for an anti-obesity agent during year
4 2011. The vast majority of these patients received a
5 prescription for phentermine. Later on in this
6 presentation, I will provide the patient demographics
7 for three main anti-obesity products of interest:
8 phentermine, sibutramine, and orlistat.

9 I will now move on to describe dispensed
10 prescription analysis by payment methods and prescriber
11 specialties. This figure shows the annual proportions
12 of dispensed anti-obesity prescriptions by payment
13 method. Over the time period examined, prescriptions
14 paid for by cash decreased, while those paid for by
15 third-party payers increased until, eventually, they
16 each accounted for approximately 50 percent of the
17 total during year 2011. The proportion of
18 prescriptions paid by Medicaid is consistently low
19 throughout this time period examined.

20 The charts represented here will show the
21 proportion of dispensed anti-obesity prescriptions by
22 prescriber specialty. During year 1991, around 72

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

33

1 percent of prescriptions dispensed were written by
2 primary care prescribers, which include general
3 practice family medicine, doctor of osteopathy, and
4 internal medicine, and around 10 percent by
5 obstetricians and gynecologists.

6 During year 2011, around 71 percent were
7 written by primary care prescribers, which include the
8 specialties mentioned previously as well as nurse
9 practitioners and physician assistants. During both
10 years, pediatric specialty accounted for around 1 to 2
11 percent of total dispensed prescriptions.

12 SDI's Physician Drug and Diagnosis Audit,
13 PDDA, provided reports of anti-obesity agent use and
14 its association with the patient's body mass index.
15 PDDA is a monthly survey of office-based prescribers
16 that provides descriptive information on patterns and
17 treatment of diseases encountered in their practices
18 throughout the U.S. These data are projected to
19 reflect national prescribing patterns in the office-
20 based practice setting.

21 Cumulative from year 1991 through 2011, the
22 body mass index was obtained for patients who had an

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

34

1 office visit where an anti-obesity was mentioned.
2 These data are provided in terms of drug occurrences,
3 where an intended prescription or sample for an anti-
4 obesity agent was issued for patients. Bearing in mind
5 that 20 percent of BMI were unknown, of those office
6 visits where an anti-obesity agent was issued, at least
7 76 percent of visits had a reported BMI of 25 and
8 greater.

9 I will provide the patient demographic
10 information for three anti-obesity products of
11 interest, phentermine, sibutramine, and orlistat, for
12 years 2008 through 2011 annually and cumulatively.

13 We used Wolters Kluwer Health's Source Lx
14 database to obtain demographic information for patients
15 who had a prescription claim for an anti-obesity
16 medication, as well as their concurrent drugs and
17 diagnoses.

18 This is a longitudinal patient data source,
19 which links diagnosis with prescription claims from
20 commercial plans, Medicare Part D plans, cash, and
21 Medicaid claims. Claims from hospital and physician
22 practices include over 190 million patients with ICD-9

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35

1 code histories, of which nearly 91 million prescription
2 drug patients are linked to a diagnosis.

3 This figure shows the number of patients with
4 a claim for orlistat, phentermine, and sibutramine by
5 year. This demonstrates that during each year,
6 phentermine is driving the utilization patterns of the
7 anti-obesity products examined.

8 This figure shows the proportion of patients
9 with a prescription claim for an anti-obesity agent
10 product by gender. Phentermine prescription claims
11 showed a greater proportion of females compared to the
12 other products shown here. Orlistat showed a greater
13 proportion of males compared to these other products.

14 This figure shows the proportion of patients
15 with a prescription claim for each product by age.
16 When comparing across products, a greater proportion of
17 patients with an orlistat claim were aged 65 years and
18 older, compared to phentermine and sibutramine. There
19 were a greater proportion of patients aged 17 to 44
20 years with a phentermine or sibutramine prescription
21 claim compared to those aged 17 to 44 years with an
22 orlistat claim.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

36

1 I will now describe concurrent drug-drug and
2 concurrent drug diagnoses with orlistat, phentermine,
3 and sibutramine. To assess comorbid conditions, we
4 examined concurrent drugs by overlapping day's supply,
5 with prescription claims for antihypertensive and
6 antiarrhythmic medications, anti-diabetic medications,
7 lipid disorder medications, and antiplatelet
8 medications from year 2008 to year 2011.

9 Also, we examined concurrent diagnoses with
10 orlistat, phentermine, and/or sibutramine using ICD-9
11 codes commonly used for arrhythmia, congestive heart
12 failure, diabetes, hypertension, ischemic heart
13 disease, lipid disorders, and stroke any time prior to
14 the anti- obesity prescription claim back to January 1,
15 2002 and any time post the date of the anti-obesity
16 prescription claim through December 31, 2011.

17 This figure shows the concurrency rates of
18 prescription claims for orlistat, phentermine, or
19 sibutramine, with claims for a drug product in the
20 following drug market categories of interest. For all
21 three products examined, there were higher rates of
22 concurrency with an antihypertensive, antiarrhythmic

1 medication and with lipid disorder medications,
2 moderate to low rates of concurrency with diabetes
3 medications and antiplatelet medications.

4 This figure shows the concurrency rates of
5 prescription claims for orlistat, phentermine, or
6 sibutramine ICD-9 codes of interest. For all three
7 products examined, there were higher rates of
8 concurrency diagnoses of diabetes, lipid disorder, and
9 hypertension. There were moderate to low rates of
10 concurrency for arrhythmia, ischemic heart disease,
11 congestive heart failure, and stroke.

12 For the concurrent drug analysis, indications
13 for use were not known for the grouped concurrent
14 medication classes. For example, for those products
15 grouped under antihypertensive and antiarrhythmic
16 medications, and those labeled antiplatelet
17 medications, these products may be used for other
18 conditions than the grouped category.

19 Levels of other uses or off-label uses were
20 not available. For the concurrent diagnoses analyses,
21 medical claims with selected diagnoses were found for a
22 subset of patients with an anti-obesity prescription

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38

1 claim at about 34 percent. These documented diagnoses
2 may be rule-out diagnoses and may not indicate true
3 comorbid conditions of the patient.

4 For all of the analyses, disease severity was
5 not delineated and other settings in which these
6 products were dispensed or administered were not
7 captured, including mail-order settings. No
8 statistical tests were performed to determine
9 statistically significant changes over time.

10 In summary, the number of anti-obesity
11 prescriptions dispensed increased by 43 percent from
12 1991 to year 2011. Approximately 2.7 million patients
13 received an anti-obesity medication during year 2011.
14 Phentermine had the market lead over the entire time
15 period examined. Females accounted for the majority of
16 anti-obesity product utilization. Orlistat showed a
17 greater proportion of use in those aged 65 years and
18 older compared to phentermine and sibutramine.
19 Phentermine in particular showed a comparatively larger
20 proportion of use in those aged 17 to 44 years.

21 Anti-obesity medications are prescribed
22 mostly by primary care providers, and most drug-use

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

39

1 mentions for anti-obesity agents were associated with
2 overweight and obese patients. There were high to
3 moderate rates of concurrency with diagnosis claims for
4 diabetes, lipid disorders, and hypertension, and for
5 patients taking antihypertensive and antiarrhythmic
6 medications, and lipid disorder medications. There
7 were moderate to low concurrency rates with diagnoses
8 claims for arrhythmia, ischemic heart disease,
9 congestive heart failure, and stroke, and for patients
10 taking diabetes medications and antiplatelet
11 medications.

12 Amongst comorbid conditions analyzed,
13 diabetes, lipid disorder, and hypertension appear to be
14 the conditions most often seen in patients taking anti-
15 obesity medications. Further study with medical record
16 validations is required to determine the true
17 prevalence of concurrent disease states and drug use.

18 That concludes my presentation. And next,
19 Dr. Christian Hampp will provide a summary of duration
20 of use.

21 DR. HAMPP: Good morning. My name is
22 Christian Hampp, and I will present to you our duration

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40

1 of use analysis. We included in our analysis the three
2 most commonly used prescription anti-obesity drugs
3 during our observation period. These are phentermine,
4 orlistat, and sibutramine.

5 To assess if the database and our algorithm
6 are able to detect long-term use when present, we
7 included two comparator drugs. These are captopril and
8 repaglinide. Among these five drugs, only phentermine
9 is indicated for short-term use and there is no
10 limitation on duration of use on the other study drugs.

11 We used data from the Wolters Kluwer Pharma
12 Solutions Source Lx database from 2002 to 2011. The
13 database contains prescription claims from various
14 payer types, including cash. It represents 172 million
15 unique patients and dispensings from 27,000 pharmacies,
16 including mail order. These data are not nationally
17 projected. For data cleaning, we had to exclude 7.2
18 percent of patients with unknown gender or date of
19 birth, duplicate claims, or dispensing for zero for
20 more than 90 days of supply.

21 Here is how we defined episodes of use. An
22 episode was a string of dispensings not interrupted by

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41

1 gaps in supply of more than 15 days. This illustration
2 shows the resulting episode based on the first three
3 dispensings. Because the dataset was based on
4 dispensings only and does not include eligibility
5 information, we had to make sure that an observed
6 episode was not truncated by patients entering or
7 leaving the database. Therefore, we will require some
8 pharmacy activity during 180 days before and after the
9 episode in question. If that occurred, we assume that
10 we would have detected any prescription of interest
11 that should have been part of the episode. We
12 calculated duration of an episode as the last day of
13 supply of the last dispensing minus the fill date of
14 the first dispensing, plus one.

15 In the sensitivity analysis, we extended the
16 allowed gap between two prescriptions to 30 days and we
17 considered stockpiling. That means that in the case of
18 two overlapping prescriptions, we shifted the second
19 one so it starts after the supply of the first
20 prescription was exhausted.

21 Here is how we counted. You can see a
22 hypothetical patient who entered the database in 2002

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

42

1 and stayed until the end of the study period. The
2 patient had regular pharmacy activity, except in an
3 early period, as indicated by the question mark. The
4 three blue bars denote three episodes of anti-obesity
5 drug use.

6 For the duration of use analysis, we only
7 included fully-observed episodes, that is episodes with
8 prescription activity in the 180 days before and after
9 the episode. We would not have considered this episode
10 because we don't know when it started. Similarly here,
11 the episode was still ongoing and we would not have
12 considered this one, either.

13 We would have considered this episode because
14 it was surrounded by pharmacy activity. Between 64
15 percent and 79 percent of all observed episodes will
16 fit the criteria for being included in the duration of
17 use analysis. However, when we counted the number of
18 episodes, we would have counted all of them because we
19 do know that they occurred. We are just not sure about
20 their length. We have to be aware that our analysis
21 does not give a lifetime perspective because we don't
22 know what happened before or after our study period.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

43

1 Here are our results, first on demographics.
2 We included between 230,000 and 1.36 million users of
3 each drug. Similar to what you saw in the previous
4 presentation, about 80 percent of anti-obesity drug
5 users were women, which is true for a little more than
6 half of comparator drug users. The average age of
7 anti-obesity drug users ranged from 41 to 47 and users
8 of orlistat were the oldest. As expected, users of
9 comparator drugs were much older.

10 These are results on the level of
11 dispensings. On average, anti-obesity drug users
12 obtained between 3 and 3.6 dispensings, but this
13 distribution is skewed, as you see with the smaller
14 median. Comparator drug users had many more
15 dispensings. The vast majority of all dispensings
16 contained 30 days of supply. Most dispensings were
17 filled in a retail pharmacy and were predominantly paid
18 by insurance.

19 I want to point out that almost half of
20 phentermine dispensings were paid in cash and that
21 Medicaid paid for proportionally more orlistat than for
22 other anti-obesity drugs.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

44

1 These are the numbers of episodes. Between
2 half and two-thirds of anti-obesity drug users had only
3 one episode. On average, each user had about two
4 episodes, but this distribution is skewed again, as you
5 see in median and upper quartile. Users of comparator
6 drugs had, on average, one more episode.

7 In blue, you see results from the sensitivity
8 analysis. With longer gaps and stockpiling considered,
9 you would expect somewhat fewer but longer episodes.
10 In fact, we see that the proportion of patients with
11 one episode increased to some degree and the average
12 number of episodes went down. There was no change in
13 median and upper quartile for anti-obesity drugs, but a
14 reduction for the comparator drugs.

15 For the duration of use analysis, we picked
16 the longest episode within each patient. This Kaplan-
17 Meier plot shows you the proportion of patients who
18 were persistent according to duration of use. The
19 lower three curves indicate anti-obesity drugs. You
20 see that only 40 to 50 percent of anti-obesity drug
21 users had an episode with more than 30 days of
22 duration. Only about one-quarter had an episode with

1 more than 90 days of duration.

2 At this point, one-half to two-thirds of
3 comparator drug users were still persistent. Only 10
4 percent of anti-obesity drug users stayed on for more
5 than 180 days and very few beyond one year.

6 This is the same information in numbers. The
7 mean duration of the longest episode ranged from 66 to
8 73 days for anti-obesity drugs and much longer for
9 comparator drugs. Again, this distribution is skewed
10 as indicated by the shorter median duration. As shown
11 on the previous slide, about half of anti-obesity drug
12 users took them for 30 days or shorter, another quarter
13 between 31 and 90 days, and a quarter for more than 91
14 days, including 1 or 2 percent who took them for more
15 than one year.

16 Once again, the sensitivity analysis. As
17 expected, the mean and median duration increased, and
18 the different categories of duration shifted to some
19 extent towards longer use. Still, only a quarter to a
20 third of patients used anti-obesity drugs for more than
21 three months and only 2 to 4 percent for more than one
22 year.

1 Next, we investigated if patient
2 characteristics were associated with duration of use.
3 This bubble graph shows the proportion of female users
4 within each drug. Each bubble denotes one category of
5 duration of use and the size of the bubbles corresponds
6 to the size of the categories. The fourth bubble for
7 each anti-obesity drug is so small because use beyond
8 360 days was uncommon.

9 On this graph, you see that anti-obesity
10 drugs had a higher proportion of females in comparator
11 drugs and that for all drugs, longer duration of use
12 was associated with a decrease in proportion of
13 females.

14 Here, we plotted average age at the start of
15 the longest episode. As shown before, anti-obesity
16 drug users were younger than users of comparator drugs.
17 Average age increased to some degree with longer
18 duration of use.

19 Finally, this slide shows the average number
20 of other prescription drugs per calendar as a crude
21 measure of general health. As expected, in diabetic
22 patients, repaglinide users used more prescription

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

47

1 drugs than other users of anti-obesity drugs or
2 captopril. Within each drug, we did not find a clear
3 association between duration of use and the number of
4 prescription drugs taken per calendar year.

5 Our study has several limitations. First, we
6 were only able to count prescriptions dispensed in
7 contributing pharmacies. If patients filled
8 prescriptions in two different pharmacies during the
9 same episode, we would have missed dispensings if the
10 second pharmacy did not contribute to the database.

11 Limited research showed that about 35 percent
12 of patients used more than one pharmacy at the same
13 time. However, because the database that we used
14 included about half of the U.S. pharmacies, chances are
15 about 50 percent that a second pharmacy would also
16 contribute to the database.

17 Next, we only had information on drug supply
18 and not actual use. This may be especially relevant if
19 patients obtained only one dispensing because in this
20 case, we would not know if the patient discontinued
21 after one dose or finished the entire supply of the
22 dispensing. For multiple dispensings, it may be more

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

48

1 realistic to assume that supply up to the last
2 dispensing was actually consumed.

3 Finally, as I indicated before, our
4 observation period was limited by study duration and
5 patient's presence in the database. And we probably
6 underestimated the lifetime number of episodes.

7 To summarize, duration of anti-obesity drug
8 use was mostly short with very few episodes. The
9 longest episode was 30 days or shorter in about half of
10 patients. Only a quarter of patients used the anti-
11 obesity drugs for longer than 90 days. Despite the
12 indication of short-term use for phentermine, duration
13 was similar to other anti-obesity drugs and a quarter
14 to a third of patients used them for longer than 90
15 days.

16 Finally, longer duration of anti-obesity drug
17 use was associated with a somewhat smaller proportion
18 of females, somewhat older age, and we found no clear
19 association of duration of use with the number of
20 prescription drugs as a measure of general health.

21 That concludes my presentation. Thank you.

22 DR. THOMAS: We will now take questions from

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

49

1 the panel. Please raise your hand, and we'll recognize
2 you from the chair.

3 Dr. Cooper?

4 DR. COOPER: I have a question for Dr.
5 Golden. On slide 20, actually, of your presentation, on
6 page 10 of our packet, you talked about a special
7 category of drugs where these weight loss drugs might
8 be used in situations where there's drug-associated
9 weight gain. One of the drugs that comes to mind,
10 obviously, is our antipsychotic medications, and that
11 would be presumably the scenario you're describing. We
12 know that these antipsychotics have their own
13 cardiovascular risk for sudden cardiac death and other
14 cardiovascular outcomes.

15 Do you all have a feeling for how commonly
16 that occurs, either from the data sources that Dr.
17 Borders- Hemphill or Dr. Hampp used, or just from your
18 understanding of how commonly this is, this co-
19 prescribing occurs?

20 DR. GOLDEN: I really don't have a feeling
21 for how common co-administration is. There's one
22 approved drug right now to treat obesity long term and

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

50

1 that's orlistat. So I'm sorry. I don't have those
2 numbers.

3 DR. THOMAS: Dr. Proschan?

4 DR. PROSCHAN: Yes. On page 11 of what Dr.
5 Golden presented, the first row says, "Percent
6 completed, one year." So these things are around 50
7 percent. The definition of completed, you're talking
8 about they came back for all weight measurements, or
9 they stayed on the drug, or what?

10 DR. GOLDEN: I don't believe that that
11 includes patients who were brought back for weight. So
12 that is -- I believe, Dr. Craig -- correct me if I'm
13 wrong, but that is a patient who came back -- who
14 stayed in the study. So 50 percent completed the study
15 and had weight measurements.

16 That's what you're asking about, slide 22?

17 DR. PROSCHAN: I'm not sure what the number
18 is. Twenty-two.

19 DR. GOLDEN: Yes.

20 DR. PROSCHAN: Yes. I think in these trials
21 they really need to spend a lot of time at the
22 beginning with the patient and tell them that, no

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

51

1 matter what, please come back for the weight
2 measurements, because with 50 percent not coming back,
3 it's really hard to make an evaluation of efficacy.

4 DR. GOLDEN: Yes. I can't speak to whether
5 those patients who discontinued were brought back at
6 one year. So I can't speak to that specific program.
7 I can say that even in programs where they do request
8 that all patients come back, you're only still getting
9 a self- selected group of patients, so you're still not
10 getting the full -- you know, the entire randomized
11 group. I mean, you would think that it might not be
12 that difficult to just come back for a weight at the
13 end of the trial, but unfortunately, it is difficult to
14 get patients to come back.

15 DR. THOMAS: Dr. Hendricks?

16 DR. HENDRICKS: I don't have questions, but I
17 have a couple of comments. One, I encourage the
18 committee to get away from using the term "cosmetic"
19 for using anti-obesity drugs in patients whose BMI is
20 lower than the indication.

21 We know with respect to cardiovascular
22 disease that cardiovascular risk begins to go up as

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

52

1 soon as excess fat begins to accumulate. Kenchaiah at
2 Harvard showed that some years ago. We also know from
3 the group at Mayo Clinic, including Dr. Romero-Corral,
4 that if you use a BMI of 30 as a dividing point, you'll
5 miss about 50 percent of the patients that have excess
6 fat accumulation. And those patients typically have
7 some increase in cardiovascular risk.

8 When you look at the patients that come in
9 for what some people might consider cosmetic use, for
10 example, a woman that's about 5'3" or 5'4" might come
11 in because she's gained 20 pounds of weight, yet her
12 BMI is only 26. I submit to you that 20 pounds excess
13 weight on one of these women is not necessarily
14 something to worry about from a cosmetic standpoint.
15 These women are more worried about long-term health
16 risks.

17 The other comment I wanted to make had to do
18 with the fact that we're -- currently, the guidelines
19 are that we are not supposed to treat until behavioral
20 modification has failed, but behavior modification has
21 a very high failure rate. So, basically, the
22 clinicians are being told to not use obesity drugs to

1 treat until late in the progression of a chronic
2 progressive illness. From a clinical standpoint, that
3 seems to be inappropriate.

4 One final comment is you've heard the usage
5 statistics from one perspective. A couple years ago,
6 four years ago, Frank Greenway and I designed and
7 conducted a survey for the American Society of
8 Bariatric Physicians among the obesity treatment
9 specialists in America. And we found, just as this
10 study found, that phentermine was the highest, most
11 frequently used drug. And we also found that a majority
12 of the physicians that responded were using phentermine
13 off schedule in the sense that they were using it for
14 much longer durations than 12 weeks. So the majority
15 of physicians said they would continue to use
16 phentermine as long as it was effective for the patient
17 and as long as the side effects were in control.

18 So if you look at the obesity treatment
19 specialists, who presumably certainly have more
20 experience with this and perhaps more knowledge, they
21 are using phentermine long term. And so from my
22 perspective as a treating physician, I think the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

54

1 statistics that show that the obesity drugs are being
2 used long term, in a very, very low percentage of
3 population are disappointing because we know that they
4 are effective.

5 DR. THOMAS: Thank you. I'd also just remind
6 the panel that, for today, if we can try and stick to
7 questions. Tomorrow, there's plenty of time for
8 discussion during the questions themselves, so comments
9 are probably best saved for tomorrow. Thank you.

10 Dr. Brittain?

11 DR. BRITTAIN: Yes. My question's for Dr.
12 Golden. You do refer to the goal being reduced
13 morbidity and mortality. And I'm wondering sort of
14 your perspective. Do you view the weight loss endpoint
15 as a surrogate or the true endpoint?

16 DR. GOLDEN: Kind of both maybe. Can I say
17 that? I think weight is one surrogate along with other
18 biomarkers that should be going in the beneficial
19 direction, some of the things that we talked about,
20 hemoglobin A1c, blood pressure, lipids. Those are all
21 surrogates for the ultimate morbidity and mortality
22 outcome. But I do also think that weight loss in and

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

55

1 of itself is important to patients and something that
2 we think is important to obviously measure as an
3 endpoint in and of itself.

4 DR. THOMAS: Dr. Seely?

5 DR. SEELY: I had a question for Dr. Vicky
6 Borders-Hemphill. On slide 12, I was interested in the
7 high relationship between weight loss, drug use, and
8 diabetes diagnosis, but the low relationship with
9 diabetes medication use. And I was wondering how you
10 interpreted that, whether you interpreted it that we're
11 not treating patients with diabetes with medications,
12 or are we using weight loss medications as a way to
13 treat diabetes.

14 DR. BORDERS-HEMPHILL: No, I don't interpret
15 that at all in that manner. The drug-drug analyses was
16 all patients on the three anti-obesity agents who had
17 an overlapping day's supply with a diabetic medication.
18 So it's not to treat diabetes, if that's your question.

19 DR. SEELY: Well, I think that's a question
20 for us to consider, as to if we consider these weight
21 loss medications, are people prescribing them only for
22 weight loss or for some of the diabetes diagnoses that

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

56

1 don't have a typical anti-diabetic drug prescribed?

2 Are these drugs being used potentially in
3 their stead as a treatment for diabetes?

4 DR. BORDERS-HEMPHILL: If the anti-obesity
5 medications are being used to treat diabetes? Is that
6 your question?

7 DR. SEELY: No. The weight loss medications
8 are being used to treat diabetes.

9 DR. BORDERS-HEMPHILL: No. That's not what
10 we're -- the analysis was done to interpret them as.
11 So we didn't look at indications of the anti-obesity
12 medications. We just looked at concurrent use with
13 diabetes medications and the other drugs.

14 DR. THOMAS: Can I just ask something with
15 that? So during the time frames -- this is many years -
16 - some of the guidance on treatment for diabetes has
17 changed. And probably in the earlier part of the study,
18 lifestyle modification was sufficient, where later in
19 the study most people would use metformin as one of the
20 recommendations, including lifestyle.

21 Do you have any data looking at earlier in
22 the time frame that you were studying versus a later

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

57

1 example for 2007 or '08?

2 DR. BORDERS-HEMPHILL: No. For the
3 concurrent diagnosis, we only looked at the cumulative
4 time period from 2008 to 2011, and we lumped all anti-
5 diabetic medications, including insulin all the way
6 down to metformin, to determine that diabetes
7 medication cohort.

8 DR. THOMAS: Dr. Gregg?

9 DR. GREGG: Yes. I had a question from Dr.
10 Golden's presentation related to the guidance to use
11 last observation carried forward analysis. It seems
12 that in situations where there's high follow-up and
13 there's not really much difference between placebo and
14 control, that that's really going to be not very
15 biased. But in situations where the treatment group
16 has a lot more loss to follow-up, it actually seems
17 like that's going to exaggerate the difference or the
18 weight loss.

19 I'm wondering whether you have accompanied
20 that by guidance in terms of the expectations of a
21 proportion follow-up, or, for that matter, whether
22 balancing it with baseline observation carried forward,

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

58

1 which of course is going to err in the other direction,
2 or something in between; or for that matter, sort of
3 more statistical approaches that are being developed,
4 too.

5 So I'm curious as to the thinking behind
6 this. This is tough one.

7 DR. GOLDEN: I'm going to turn this over to
8 our statistical colleague.

9 DR. SAHLROOT: Todd Sahlroot, statistics team
10 leader for the diabetes group and obesity. The
11 guidance is about five years old. So at that time,
12 LOCF was more or less a standard approach to impute
13 missing data.

14 Since then, the National Academy has come out
15 with a report on recommendations for missing data in
16 clinical trials. And based on that report, we have
17 taken a more negative view of LOCF. And we've been
18 encouraging sponsors to use other approaches like
19 repeated measures, but certainly to get a better
20 understanding of the pattern of missing data. As far
21 as baseline observation carried forward, sponsors have
22 used that. We haven't actively encouraged that,

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

59

1 although I think we're going back and reevaluating how
2 we treat missing data.

3 So right now, our approach is to not
4 necessarily designate LOCF as primary, but to encourage
5 a range of approaches that might include baseline
6 observation carried forward.

7 DR. THOMAS: Dr. Hiatt?

8 DR. HIATT: A follow-up question from what
9 Dr. Brittain brought up. And that is -- it's for Dr.
10 Golden. I'd like to know a little bit more about how
11 these earlier guidances were communicated to sponsors
12 in their development programs.

13 So you clearly indicated that weight loss was
14 primary, and I understand that. And you also say that
15 there should be an association of weight loss as some
16 other measure of clinical benefit. But when you look
17 at the other development programs, it's not really
18 clear that was well assessed. So some of the
19 biomarkers are all kind of there, blood pressure, heart
20 rate, lipids, insulin sensitivity. Those were
21 consistently measured, but not integrated into sort of
22 a sense of overall risk. So it's not clear, if a drug

1 is, for example, changing one biomarker in a negative
2 way and another biomarker in a positive way, if that
3 overall is associated with improved risk.

4 So simple things like framing a risk
5 assessment of those sort of directional changes in
6 various biomarkers might have been useful, short of
7 hard events, which are hard to get in these small
8 programs. But I didn't see any of that.

9 You also mentioned, in one of your slides,
10 sleep apnea, cardiovascular disease. I suppose the
11 list could go on, DJD, these kinds of things. But it's
12 not clear that the clinical benefit was really
13 rigorously looked at beyond the primary endpoint of
14 weight loss.

15 Could you comment how sponsors were
16 instructed, in terms of these clinical trials, to look
17 at the overall benefit beyond the weight loss endpoint?

18 DR. GOLDEN: I don't know if I can comment
19 about approval of the drugs under the previous
20 guidance, just because I wasn't there. But I can say
21 that weight was and is currently the primary endpoint.

22 If you want to use sibutramine as an example,

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

61

1 I know that the blood pressure was noted. So that's
2 one example where maybe a biomarker was not going in
3 the direction that you would have expected based on the
4 weight change, and that was discussed pre-approval.

5 So I think that the same issues and concerns
6 have been communicated. It's just experience over time
7 has made us re-think how important associated
8 biomarkers might be.

9 DR. THOMAS: Dr. Konstam?

10 DR. KONSTAM: Yes. Hi. First, just one
11 comment about last observation carried forward. I
12 guess I would think that it would be severely
13 problematic with a set of drugs with a known and
14 concerning attrition rate of benefit and then trials
15 where the dropout rate is extremely high. I just would
16 assume that you would really want to go away from last
17 observation carried forward in trying to determine
18 duration of efficacy.

19 Then the clarification point that I just
20 wanted is, what does one-year duration mean in the
21 current guidance? Is that one-year duration on drug?
22 Is that one-year duration of efficacy? What does one-

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

62

1 year duration mean?

2 DR. GOLDEN: One-year duration from the time
3 of randomization for 12 months. So on drug --

4 DR. KONSTAM: On drug.

5 DR. GOLDEN: Right. So I guess it depends on
6 which analysis you're going to be using. So you're
7 going to follow everybody for one year. And if you're
8 going to be using last observation carried forward and
9 they drop out at six months, then that six months will
10 be imputed for the year.

11 DR. KONSTAM: I guess I just was wondering
12 what your view or the agency's view of what does that
13 guidance statement mean. When you're speaking to
14 companies or you're evaluating the NDA, are you
15 expecting a certain -- so you're looking for 3,000
16 patients receiving active drug --

17 DR. GOLDEN: Randomized.

18 DR. KONSTAM: -- randomized. And are you
19 looking for a certain number of those to be on drug for
20 one year?

21 DR. GOLDEN: Oh, I see. We sort of
22 anticipated approximately 50 percent dropout. So I

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

63

1 guess, then, you would think 1500 approximately would
2 be on drug at the end of 12 months for a full 12
3 months.

4 DR. KONSTAM: So you're looking for 1500
5 patients receiving drug for a year?

6 DR. GOLDEN: For a year.

7 DR. KONSTAM: That's what that means.

8 DR. GOLDEN: Yes.

9 DR. KONSTAM: Thank you.

10 DR. THOMAS: Dr. Rasmussen? Go ahead.

11 DR. RASMUSSEN: No. I don't think I had a
12 comment at this stage. I would just like to comment
13 that I think we've seen very nice data that shows the
14 overlap between the study populations and those who
15 actually seek treatment in a real-life setting.

16 I do have one question, which is do we have
17 any idea of whether real-life efficacy dictates
18 duration of use? I know these databases may not be the
19 best to examine that, but you would expect that in real
20 life, if people have greater efficacy, they would stay
21 on treatment for longer.

22 DR. HAMPP: Unfortunately, we don't have any

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

64

1 such data.

2 DR. THOMAS: Dr. Yanovski?

3 DR. YANOVSKI: I think this question is for
4 Dr. Borders-Hemphill. If I'm understanding the data on
5 our page 8, so I guess slide 16, for age, and
6 considering that the vast majority of patients are
7 female, it sounds like somewhere between a third and
8 half of all subjects, all patients who actually take
9 these drugs, are women of reproductive age.

10 Do we have any information about what
11 percentage actually are at risk then to have a fetus
12 affected by drugs that they would be taking?

13 DR. BORDERS-HEMPHILL: So the question is
14 whether or not we have the data to determine whether or
15 not these females are at risk? The utilization data
16 would not necessarily show that. It's just the age
17 breakdown of these patients.

18 DR. THOMAS: Dr. Spruill?

19 DR. SPRUILL: I didn't have a question, but I
20 have a comment. And I was thinking I was particularly
21 struck by the slide on page 5, that talked about
22 prescriptions. And I was surprised that 72 percent of

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

65

1 providers were primary care providers. And that was
2 surprising to me.

3 I made the assumption that it would be a
4 specialty that would do this. But when I looked at
5 this slide -- I think it's slide 9, and I think you
6 talked about 72 percent were primary care providers.
7 And I was curious about if they were in private
8 practice or in clinical settings.

9 DR. BORDERS-HEMPHILL: These are office-based
10 physician settings, and they're by the specialty of
11 their degree. I guess that's what you could say. So
12 these are outpatient, office-based settings.

13 DR. SPRUILL: Okay.

14 DR. BORDERS-HEMPHILL: Are you trying to get
15 to whether or not these are weight loss clinics?

16 DR. SPRUILL: Or if they were specialties.

17 DR. BORDERS-HEMPHILL: Like an anti-obesity
18 specialty?

19 DR. SPRUILL: Yes. Because when I see this,
20 I'm thinking, is this saying primary care providers, a
21 general practitioner versus a specialist?

22 DR. BORDERS-HEMPHILL: What this should be

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

66

1 interpreted as is that the primary care physicians
2 include your general practice, family medicine,
3 osteopathy, and internal medicine as a group. And then
4 in 2011, primary care specialties -- or primary care
5 providers, should I say, included also the nurse
6 practitioners and the physician's assistants. Now,
7 whether or not these are being prescribed through anti-
8 obesity clinics or weight loss clinics, that is not to
9 be determined by this type of data, as it's not based
10 on the weight loss clinic setting. It's based on that
11 physician's specialty.

12 DR. THOMAS: I'd like to ask a follow-up
13 question. Maybe Dr. Hampp can help answer this as
14 well. The adherence to medications has a variety of
15 factors. Cost is one of them, including efficacy and
16 safety.

17 When you look at the prescribing patterns, or
18 dispensation patterns of the pharmacies, can you look
19 at the interaction between whether you're paying for
20 the medications, whether insurance is covering it, and
21 also the interaction potentially, for example, of
22 reproductive-age women who may become pregnant during

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

67

1 the course of the study and then are out for nine, or
2 12 months, or longer?

3 Are there any other possibilities for
4 explanations of why patients don't take these
5 medications for long periods? Or another one would be
6 the provider. For example, certain providers may have
7 more expertise, put people in behavioral programs so
8 that their patients are more likely to stay on, versus
9 other providers may not do that and may just give a
10 prescription.

11 DR. BORDERS-HEMPHILL: So the first part of
12 the question was how these prescriptions are being paid
13 for and whether or not that affects the duration of
14 use. The data that I have that showed that
15 prescriptions were, at one point in time earlier, in
16 the 1991, '90s -- they were mostly being paid for by
17 cash, but third-party providers are increasingly
18 providing payment for these medications.

19 Now, whether or not that affects the duration
20 of use, I'm not sure if Dr. Hampp had looked at that.
21 And then you asked the question about --

22 DR. THOMAS: The other one would be the type

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

68

1 of specialty. Does that have an interaction with the
2 duration of use? And then, because many of the
3 patients who are taking this would be reproductive-age
4 women, are there gaps, for example, people who are off
5 it for 9 to 12 months and then suddenly retake it
6 because they might have gotten pregnant during the
7 course of their treatment?

8 DR. BORDERS-HEMPHILL: With regards to
9 whether or not women became pregnant -- and I think
10 that was part of the other question about will these
11 women be at risk taking these medications -- we don't
12 have the data to determine pregnancy in these datasets.

13 DR. THOMAS: Could you use a surrogate like,
14 looking at women of reproductive age, would you see
15 interval gaps, or 12 months, and then resumption? You
16 couldn't actually tell that they were pregnant, but you
17 could make an inference.

18 DR. HAMPP: I'm going to start with the first
19 part of your question on whether payment type affects
20 duration of use. And we did not see a clear
21 association. In fact, what we saw in some episodes,
22 that payment type is mixed. So patients would have a

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

69

1 dispensing paid by insurance and the next dispensing in
2 cash. That was not the rule, but it happened in quite
3 a number of cases.

4 Also, you saw that phentermine had a much
5 higher proportion of cash payments than other drugs and
6 we did not see a difference in duration of use between
7 phentermine and other drugs. So we cannot confirm that
8 there is a difference between payment type and duration
9 of use.

10 We did not look at pregnancy as far as breaks
11 in episodes are concerned, but we did see that about
12 two- thirds of patients only had a single episode. So
13 for those, this would not apply anyways.

14 With regard to -- your second question was
15 about provider specialties and duration of use. We did
16 not analyze those.

17 DR. THOMAS: Thank you.

18 Dr. Bergman?

19 DR. BERGMAN: Yes. I have a question for Dr.
20 Hampp. So to the outsider, somebody just showing up
21 like I am, the duration of use is remarkably short.
22 And one assumes that the purpose is to get some weight

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

70

1 loss, which then could be converted to some other
2 approach.

3 But probably, the overall question is, what
4 is the overall effect of these agents to obesity
5 overall? If they didn't exist, would there be any
6 difference in the overall picture of obesity for the
7 country or the United States? Are they really having
8 an impact? Because the duration of use is so short, and
9 probably the recidivism with respect to obesity may be
10 very great. So it could be the overall actual effect
11 is very small, from a public health perspective.

12 So that's my question.

13 DR. HAMPP: I could only speculate. We saw
14 in the number of patients who use anti-obesity drugs,
15 only about 2.7 million in 2011 used prescription anti-
16 obesity drugs. And that's out of two-thirds of the
17 population are overweight or obese, but I don't know
18 about the adult population. But it's way more than 100
19 million. 2.7 million take OM prescription anti-obesity
20 drugs. So the impact of them on the national obesity
21 epidemic is probably negligible.

22 If we look at duration of use, I'm not sure

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

71

1 how much of a reduction in weight one experiences when
2 one takes a 30-day prescription. Clinical trials
3 indicate that there are some, but we don't know how
4 many doses of a 30-day prescription they have actually
5 taken. If somebody doesn't like the side effects early
6 on, they will stop.

7 DR. THOMAS: Dr. Colman?

8 DR. COLMAN: Yes. I wanted to respond to Dr.
9 Konstam's comment earlier. It was pretty common in the
10 '90s, when obesity drugs were developed in the '90s,
11 where you would see, in a one-year trial, 50 percent of
12 subjects dropping out of both treatment groups before
13 the end of the study. And oftentimes, that would be
14 the last that you heard of those individuals.

15 So as we proceeded in working with companies,
16 the first thing we wanted to encourage them to do is,
17 if someone drops out of the trial, or they drop off
18 study drug, please try to keep them in the study and
19 continue to follow them so that we can get the
20 appropriate data up until the time that they would have
21 normally completed the study. And I think we've made
22 some headway in that respect.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

72

1 The other thing that is a positive sign is
2 one of the more recent obesity drug applications that
3 we reviewed, I think, through diligence on the part of
4 the company and the folks who are running the trials,
5 the dropout rate over the course of a year was more
6 like 30 percent rather than 50 percent.

7 So I think you can, with the proper approach,
8 increase retention on study drug, and then if people do
9 go off study drug, certainly get vital status on those
10 people who drop out at the end of the trial.

11 DR. KONSTAM: Well, thank you for that. I
12 guess, in the simplest terms, I just was curious what
13 you all meant in terms of your guidance statement about
14 one year, and what does that mean to you, and what does
15 that mean to companies. So I guess in the simplest
16 terms, I was just trying to figure out what that
17 actually meant.

18 But then, picking up on your comments --
19 let's use different terms. Study drug discontinuation
20 is a big problem for safety assessment, obviously,
21 because you start regressing to no effect and that's a
22 big problem. And here I think it sounds like there's

1 also an efficacy problem because there's a concern
2 about attrition of effect. And if you're following
3 patients out after they've discontinued study drug,
4 well, then you might say, okay, well, that's
5 disadvantaging the efficacy, so that's okay, that's a
6 conservative assessment unless there actually is an
7 attrition of drug effect over time that you're missing.

8 So if, in fact, the patient were continued on
9 drug for a year, they might have less of a benefit than
10 you would see by a last observation carried forward
11 measurement, based on a measurement done at six months.

12 DR. COLMAN: Right.

13 DR. KONSTAM: So it just seems like it's a
14 big issue in this field and something that we ought to
15 come to consensus on.

16 DR. COLMAN: This is a topic of discussion
17 for tomorrow, so I suspect we'll talk more about it.

18 DR. THOMAS: We'll go onto our next -- Dr.
19 Temple?

20 DR. TEMPLE: Along the same lines -- and
21 maybe there will be more discussion tomorrow -- there
22 were two endpoints that you used here. One is the mean

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

74

1 change, which raises all these LOCF questions. But the
2 other was achieving the fraction of patients who
3 achieve a 5 percent weight loss.

4 Could you say when that is measured? Is that
5 measured the last time you see them, or is that the
6 maximum loss they get? How do you do that? And that's
7 a little harder to do LOCF to.

8 DR. GOLDEN: But the last time you see them
9 is the primary analysis.

10 DR. TEMPLE: So that really would be LOCF, if
11 you like.

12 DR. GOLDEN: Yes.

13 DR. TEMPLE: And I guess the presumption is,
14 if they go off therapy, their, probably, weight goes
15 back up.

16 DR. GOLDEN: Right.

17 DR. TEMPLE: Okay. Yes.

18 DR. THOMAS: We will have time for more
19 questions later today and also for tomorrow for some of
20 the speakers. So we'll continue on with our next
21 speaker, Dr. Eckel.

22 DR. ECKEL: It's good to be with you this

1 morning. And in many ways, I feel like I'm bringing
2 coal to Newcastle here with this panel of distinguished
3 scientists and physicians. In many ways, it seems like
4 what I'm going to be presenting today is science and
5 medicine you know quite well. But I'm going to be
6 taking broad strokes this morning, overviewing the
7 topic of the pathophysiology of obesity and
8 cardiovascular disease.

9 So if we look at the relationship between
10 obesity and cardiovascular disease -- and we're looking
11 now at data coming from a study that was not intended
12 to look at body weight and cardiovascular disease, the
13 Cancer Prevention Study II -- we see convincing
14 evidence from a large number of individuals that
15 ultimately looking at non-smokers without known heart
16 disease, that ultimately BMI very importantly relates
17 to an increased likelihood of cardiovascular disease
18 mortality. This curve starts to go up at a BMI of
19 about 25 and then becomes more exponential at levels
20 above 30, as we currently defined obesity.

21 Now, again, broad strokes linking the
22 pathophysiology of obesity to CVD. We've got to

1 believe that ultimately, the insulin resistance
2 paradigm is part of that. And when we think of insulin
3 resistance or the metabolic syndrome in other
4 terminology, we think of an interaction between
5 hypertension, dyslipidemia, inflammatory kind of risk,
6 and also that related to diabetes.

7 So this is feeling the elephant, if you will,
8 and you may not like the metabolic syndrome, but it's
9 an elephant here to stay. It's amazing. In papers on
10 nature and cell, you see people relating to the
11 metabolic syndrome. And although there has been
12 substantial controversy about the metabolic syndrome,
13 this ultimately is an insulin resistance paradigm that
14 I think, in the setting, particularly of upper-body
15 obesity, Mike, or in fact visceral adipose tissue
16 excess, we see an increased likelihood of ultimately
17 the comorbidities we associated with obesity.

18 Now, let's just pause here a second and look
19 at the role of adipose tissue and adipose tissue
20 distribution of the metabolic syndrome. So what we're
21 looking at in this panel is, on the left, adipose
22 tissue function, including insulin action,

1 catecholamine action, leptin production, PAI-1
2 production, angiotensinogen, IL- 1 representing the
3 pro-inflammatory cytokines, and the production of
4 adiponectin.

5 Ultimately, we look at insulin actions as a
6 good thing. Ultimately, the production of adiponectin
7 is a good thing. And ultimately, leptin, which signals
8 to the brain ultimately body weight regulation, is
9 probably a hormone that likely is there for starvation
10 dynamics and not so much for excess body fat. But look
11 at the tissues in terms of adipose tissue distribution
12 of visceral fat versus subcutaneous fat, in terms of
13 where these compounds are produced.

14 So we are working in an area now; we're
15 increasing subcutaneous adipose tissue and redepositing
16 fat from the central area, including the liver, the
17 visceral depot to subcutaneous sites, and may
18 ultimately be a strategy by which cardiovascular risk
19 may be modified. So keep in mind here, adipose tissue
20 distribution has a lot to say about the metabolic
21 syndrome. It's one of the five components and, in
22 addition, has a lot to do with cardiovascular disease

1 risk.

2 Time doesn't permit me to review an extensive
3 amount of literature, but here, today, we're looking at
4 the Nurses' Health Study with a follow-up of eight
5 years, where we're looking at the effect of body mass
6 index in tertiles versus waist girth in tertiles. And
7 as you see there, we have a staircase in both
8 directions, but if you will, that staircase is much
9 steeper for women who put their excess body fat
10 abdominally.

11 Another thing I think to keep in mind is, a
12 pelvic adipose tissue distribution in women,
13 particularly pre-menopausally, is often not associated
14 with cardiovascular disease risk. But after the
15 menopause, we see some shifting in adipose tissue depot
16 deposition and that presumably could be part of the
17 reason we see abdominal obesity, particularly central
18 obesity, associated with more risk for cardiovascular
19 disease.

20 Now, if we look at the relationship between
21 visceral adipose tissue and insulin action, we see this
22 nice curvilinear relationship. And Richard Bergman

1 will like the next slide in terms of the disposition
2 index. I think it's important to remind this group --
3 and many of you know this well -- that ultimately
4 diabetes is not insulin resistance.

5 One thing I asked the house staff and
6 students when I attend on the general medical ward is
7 what is diabetes, and the answer is always insulin
8 resistance. Well, diabetes is not insulin resistance.
9 Diabetes is a defect in beta cell function.

10 So what we see is when people fall off the
11 curve in terms of this curvilinear relationship between
12 beta cell function and insulin action, more insulin
13 sensitivity here, more beta cell function here, when
14 you fall off the curve, you develop impaired glucose
15 tolerance and then ultimately type 2 diabetes.

16 Now, you say what's the reason for bringing
17 that up here? I think it's a very important thing
18 because, when we get into type 2 diabetes, the
19 cardiovascular disease risk really is compounded on top
20 of that related to obesity in type 2 diabetes.

21 So I'm just going to share with you a diagram
22 that, ultimately, we've used for years, published in

1 the last review on the metabolic syndrome a number of
2 years ago. When adipose tissue expands, it drives the
3 production of triglyceride-rich particles in the liver.
4 We'll come back to that momentarily. But in addition,
5 this pro-inflammatory component of the insulin
6 resistance syndrome not only has systemic effects by
7 these cytokines going to skeletal muscle and modifying
8 insulin sensitivity, but going to the liver and also
9 probably driving much of the insulin resistance in the
10 liver.

11 But the cytokines also have a local paracrine
12 effect where they modify insulin sensitivity in the
13 adipose tissue depot per se. And then ultimately, we
14 find that the driving force of excess free fatty acids
15 reaching the liver and the pro-inflammatory cytokines
16 probably involves locally at the adipose tissue level
17 and that at the level of the liver to create the pro-
18 thrombotic state, certainly a component of the
19 metabolic syndrome in cardiovascular disease risk in
20 patients with obesity.

21 Then we have a reduction in the production of
22 adiponectin, which is an anti-inflammatory cytokine.

1 And ultimately, reductions in adiponectin probably
2 plays some role in modifying insulin sensitivity
3 systemically and the reduction in levels probably
4 contributes also to the systemic insulin resistance.

5 Then finally, we see effects directly on the
6 arterial wall that probably is the hypertension
7 component of insulin resistance, but Ellen and others
8 in the room may, in fact, have other mechanisms which
9 clearly take place. But the link between insulin
10 resistance and endothelial dysfunction from either pro-
11 inflammatory cytokines or excess free fatty acids
12 probably play an important role in how the vascular
13 endothelium behaves. And ultimately, in many of these
14 things, we associate insulin resistance with
15 hypertension to cardiovascular disease risk.

16 Now, let's turn to the lipid abnormality that
17 we see in patients with obesity and insulin resistance.
18 Basically, this is due to an increased production of
19 atherogenic Apo B-containing lipoproteins, the presence
20 of small VLDL. More recent work epidemiologically and
21 mechanistically have related the overproduction of Apo
22 C- III E- contained VLDL, which may be particularly

1 pro- athrogenic; the ideal or remnant particles are
2 intermediate-sized particles, which were overproduced
3 in patients with obesity and insulin resistance, and
4 finally defects in removal of triglyceride-rich
5 lipoproteins.

6 Here's a slide I've added since your handout,
7 so it doesn't have a number on it. But this is a
8 diagram that I placed in an editorial in a recent paper
9 on ATVB, which now seems to associate excess adipose
10 mass directly to insulin resistance, rather than
11 driving directly to the liver from the free fatty acid
12 flux, work out of the Helsinki group in Finland,
13 ultimately driving the production of these Apo C-III-
14 containing particles, and then the defect in
15 lipoprotein lipase.

16 LPL is the rate-limiting enzyme for
17 triglyceride clearance and the C-III-containing
18 particle inhibits this enzyme. So fasting and
19 postprandial triglyceridemia mechanistically likely
20 relates to this path of biology.

21 Now, in addition, patients with obesity and
22 insulin resistance have reductions in HDL cholesterol.

1 And the reason they have reductions is, first of all,
2 the HDL or triglyceride enriched. They have less
3 cholesterol content. There's also an increase in
4 cholesteryl ester transfer protein, which tends to
5 modify the cholesterol content of HDL, transferring the
6 cholesterol from the core of the particle to Apo B-
7 containing particles.

8 Patients also have decreased HDL because
9 lipoprotein lipase is reduced, as pointed out on the
10 previous slide. And therefore, there's less production
11 of the large buoyant form of HDL II, which in fact many
12 people feel is cardioprotective.

13 Finally, because of the triglyceride content
14 of the HDL, these particles are rapidly cleared from
15 the circulation. Again, the lipid abnormality relates
16 to the insulin resistance and links obesity to
17 cardiovascular disease risk.

18 Now, in addition, we certainly have
19 modifications of inflammatory markers. Here, we're
20 looking at the relationship between acute phase Z
21 scores in the sense of insulin resistance and the
22 presence of inflammatory markers, a composite

1 underneath the area of the curve, a highly significant
2 relationship.

3 If you believe in the metabolic syndrome,
4 which again is an elephant that's here -- we can't
5 ignore it -- the number of metabolic disorders that are
6 part of the metabolic syndrome relates to increasing
7 elevations of hsCRP, the marker we often utilize to
8 assess the pro- inflammatory condition in our patients.

9 Now, metabolic syndrome is more than this.
10 And I simply share this with you because insulin
11 resistance carries a lot of other metabolic effects
12 downstream. And what relates to us here today is
13 obstructive sleep apnea, which I'll say very little
14 more about, but we certainly know patients with insulin
15 resistance, central adiposity, appear to have a greater
16 likelihood of having defects in oxygenation at night
17 due to obstruction in their airways.

18 Now, we have a building block here of
19 abdominal obesity or upper body obesity, borderline
20 risk factors that are further modified to categorical
21 risk factors, leading to an increased likelihood of
22 cardiovascular disease and related complications. And

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

85

1 ,of course, farther to the right, which you'll hear
2 more about, is the type 2 diabetes downstream scenario,
3 and then ultimately the complications we associate with
4 diabetes.

5 Now, in addition, there's a lot of other
6 abnormalities that relate diabetes to cardiovascular
7 disease. And I should point out, that initial slide I
8 showed you from the Cancer Prevention Study included
9 not only coronary heart disease, but it included
10 congestive heart failure and also included stroke. So
11 the cardiovascular disease is a big umbrella,
12 considering a number of different cardiovascular
13 diseases we associate with obesity.

14 So here's the list. Coronary heart disease,
15 we'll talk just a bit more about. Then there's the
16 whole myocardial dysfunction paradigm of diastolic
17 dysfunction initially, left ventricular hypertrophy,
18 plus or minus failure. This can occur in eccentric
19 manners, concentric manners. And then it can occur
20 from the deposition of lipid in the myocardium, per se.
21 And that certainly relates to defects in cardiovascular
22 function, particularly in the left ventricle.

1 But look at right ventricular hypertrophy.
2 Often, right heart failure comes from a mechanism that
3 we entitle pulmonary hypertension. Patients with
4 obesity have a multiplicity of factors that contribute
5 to this. Obstructive sleep apnea is the most obvious.
6 But in addition, they can have central hypoventilation,
7 the Pickwickian syndrome, less common, yet clearly part
8 of the pathophysiology.

9 Then often not appreciated is, patients with
10 obesity have phlebothrombosis. They have more deep
11 venostasis. They have clots and pulmonary
12 thromboembolic disease is often a cause of repeated
13 events that raise the pressures of the pulmonary
14 circulation and result in pulmonary hypertension. We
15 can't think about this area too little. We, in fact,
16 need to move this up on the list of causes of right
17 ventricular hypertrophy. And then there's autonomic
18 dysfunction and arrhythmias, prolonged QTc, and sudden
19 death.

20 Now, Paul Poirier, a distinguished
21 cardiologist from the Universite of Laval, and I have
22 worked very carefully with the American Heart

1 Association over the years to evolve this concept of
2 obesity and cardiovascular disease. In fact, when Ron
3 Krauss and I, in the mid-90s, wrote this call to action
4 for the AHA, we said obesity is a modifiable etiology
5 of cardiovascular disease. We didn't say a cause
6 because often obesity and all its covariates is really
7 what plays into the risk, not so much excess body fat,
8 per se.

9 But keep in mind, now, 80 percent of people
10 with obesity are insulin resistant. We all see these
11 walking- well people that are overweight or obese who
12 have normal glucose, normal blood pressures. Those
13 people deserve more study, in my opinion, to understand
14 why all obese patients don't really have insulin
15 resistance and cardiovascular disease risk. But
16 nevertheless, that's a topic for a different agenda for
17 sure.

18 So there are adaptations that occur in
19 obesity, initially, that may be somewhat favorable,
20 though interstitial fluids increase and you could
21 question the value of that. There's peripheral
22 vasodilatation, which relates to decreases in

1 peripheral resistance. And ultimately, there is still
2 -- despite the volume excess in peripheral
3 vasodilatation, there seems to be the earliest signs of
4 left ventricular end diastolic pressure increases.
5 Heart rate is often a little bit higher in obese
6 patients, and cardiac output initially is higher in
7 patients with obesity, before a lot of these other
8 pathophysiological issues enter into the equation.

9 Now, when we look at coronary heart disease,
10 I'm going to point out a couple of slides that seem
11 initially unrelated. This is the hazard rate of the
12 risk for diabetes over 17 years in healthy young adults
13 according to BMI in adolescents down here or BMI in
14 adulthood down here.

15 These are 37,000 young men in the Israeli
16 armed services who were evaluated baseline when they
17 entered the service, and then were evaluated 17 years
18 later. If we look at cardiovascular disease in adults,
19 we see that BMI in adolescence doesn't seem to have
20 much impact -- I'm sorry; we're talking about diabetes
21 -- on diabetes as much as adult BMI does.

22 But when you look at the cardiovascular

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

89

1 disease risk, look at this, BMI in adolescence stair
2 casing from right to left in terms of cardiovascular
3 disease risk. And here's BMI as an adult.

4 So the point of this slide, as we've learned
5 from Vietnam, and other experiences, the PDAY study,
6 and many of the pediatric studies that look at
7 cardiovascular disease and obesity in young people,
8 ultimately we have evidence here that obesity in
9 adolescence confers a substantial, independent risk
10 from BMI in adults for cardiovascular disease
11 development.

12 Now, when we look at other aspects of
13 cardiovascular disease, we're going to look at the left
14 ventricle predominantly but also RVH. And there are a
15 number of mechanisms that I'm not going to go into
16 great detail here today about, but cardiac myocyte
17 hypertrophy, myocardial ischemia, reduced cardiac
18 function manifested by a number of other defects within
19 the myocardium itself, cardiac arrhythmias, autonomic
20 neuropathies, the metabolic factors we've alluded to,
21 to some extent, and then actually inflammation within
22 cardiac muscle.

1 A lot of heart failure physicians and
2 scientists are working on mechanisms for heart failure
3 that link obesity to congestive heart failure, perhaps
4 even independent of coronary disease and hypertension.
5 And ultimately, these are kind of mechanistic factors
6 that relate to heart failure in the absence of a lot of
7 other contributing issues.

8 Back to hypertension for a moment. Here,
9 we're looking at individuals with a BMI of greater than
10 30 versus those compared to under 25. And we're
11 looking at a two-and-a-half-fold increase in the
12 likelihood of hypertension. These are from NHANES III
13 data. And I suspect more recent data, which I couldn't
14 find from NHANES, are probably available. But I'm sure
15 that the hypertension prevalence is at least the same,
16 if not higher, in patients with obesity versus those
17 with normal body weight.

18 As we look at other mechanisms relating
19 obesity to hypertension, other than the insulin
20 resistance paradigm, which I've already briefly
21 described, we certainly have more sodium and volume
22 retention. Patients with obesity can develop renal

1 dysfunction. And ultimately, they importantly have
2 activations of the renal and angiotensin system as
3 implied by my earlier slide, showing angiotensinogen
4 gene up regulation in adipose tissue, per se. And here
5 is simply a graphic representation of the duration of
6 severe obesity and systolic blood pressure, and the
7 duration of severe obesity and left ventricular end
8 diastolic dimension.

9 Now, if we look at the Women's Health
10 Initiative, and we look at cardiovascular disease,
11 mortality and its relationship to hypertension, these
12 are women here that were on one drug for hypertension.
13 And here are women that were on several drugs for the
14 treatment of hypertension. And if you drill down in
15 the data, these are the factors in the Women's Health
16 Initiative that related to hypertension that ultimately
17 contributed to cardiovascular disease, events, and
18 mortality. Overweight, alcohol intake, and physical
19 inactivity were the three most important predictors of,
20 ultimately cardiovascular disease development and
21 mortality in the Women's Health Initiative.

22 Now, when we turn down further in this graph

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

92

1 or slide in terms of the other things we think about in
2 patients with obesity, there are ECG changes that are
3 commonly found in obesity. And you cardiologists on
4 Jay, et al. (ph) are well aware of these.

5 But clinically significant alterations in the
6 electrocardiogram include increases in heart rate, QRS
7 interval, the QTc interval, and often false-positive
8 criteria for a diagnosis of inferior wall myocardial
9 infarction is seen in obese patients. And down the
10 list -- and I'll not review each one of these with you
11 -- are probably less clinically significant
12 relationships between obesity and the ECG. But we've
13 got to keep in mind that the ECG in patients with
14 obesity can sometimes be informative, sometimes
15 misleading, and that needs to be taken into
16 consideration.

17 But the other thing we find in obesity is the
18 potential development of more serious considerations
19 such as atrial fibrillation and late potentials. And
20 the prevalence of a number of these abnormalities
21 increases with increasing obesity. And these appear to
22 be independent of some of the downstream comorbidities

1 we associate with obesity, including hypertension and
2 diabetes. And these arrhythmias mechanistically may be
3 facilitated by a lot of the alterations we see in the
4 myocardium, per se, listed on a previous slide.

5 Now, benefits of weight reduction --
6 decreased blood volume, decreased stroke volume,
7 decreased cardiac output, reductions in pulmonary
8 capillary wedge pressure, reductions in LV mass,
9 improvement of left ventricular diastolic dysfunction,
10 a left ventricular systolic function, heart rate falls.
11 QTc interval goes down and heart rate variability
12 increases, a more normal physiological paradigm for
13 heart rhythms in patients in general.

14 Now, before I describe this slide, I want to
15 remind you that following bariatric surgery, all-cause
16 mortality is reduced. This is SOS data. These are
17 Latter Day Saints data coming out of Utah. But in
18 addition, ultimately, cardiovascular disease events are
19 reduced. And that's a recent paper from the SOS study.
20 Cardiovascular disease mortality was not reduced by
21 bariatric surgery.

22 So events are down, but cardiovascular

1 disease mortality was not down. We need to take that
2 into consideration. Now, that's an extreme weight loss
3 and I'm only using that as an example because changes
4 in left ventricular mass, and ultimately left atrial
5 volumes, and ultimately a fractional shortening are all
6 modified in patients who are having successful weight
7 loss through bariatric approaches. And here is
8 unpublished data from Paul Poirer's group, showing
9 reductions in heart rate, reductions in QT interval,
10 and ultimately QTcs.

11 So we certainly know, from the bariatric
12 approach, where we have more data after more extreme
13 weight reduction, that we modify issues that relate to
14 the cardiovascular system that presumably are going to
15 be beneficial in patients with obesity. And I think as
16 we think about drugs and how they're to be used in
17 obesity, we clearly have other issues to bring into
18 consideration. But these are the data in broad strokes
19 that relate obesity to cardiovascular disease.

20 So to conclude obesity confers an increased
21 risk for cardiovascular disease. Secondly, I think
22 insulin resistance is a major contributor to many of

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

95

1 these cardiovascular disease comorbidities. Thirdly, I
2 think hypertension is an important and major player.
3 It's somewhat difficult to see, in comparison to other
4 players, exactly how important hypertension is. But I
5 feel -- and this is an opinion -- that this is an
6 incredibly important factor and probably needs to be
7 taken into greater consideration.

8 Myocardial dysfunction is common and is both
9 biventricular and multifactorial in terms of
10 mechanisms. And finally, cardiac arrhythmias are
11 present and relate to many aspects of obesity and its
12 comorbidities, and this is something I think we should
13 not dismiss.

14 So I'm going to stop here and say thank you,
15 and I'm happy to take any questions.

16 Abraham?

17 DR. THOMAS: Thank you for your excellent
18 talk, Dr. Eckel.

19 We'll now take questions from the committee
20 in the order that you raise your hands so we recognize
21 you. Ms. McAfee?

22 MS. MCAFEE: I have a question about slide 8.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

96

1 The BMI cutoffs for the high BMI is a pretty broad
2 range, 25 to 48.8. Can you break that down a little
3 for us? I mean, is it a linear progression? Is it
4 higher? Can you just give me more information on that?

5 DR. ECKEL: No. Those are the data. That's
6 all the information -- I'm sorry -- I can give you on
7 that.

8 MS. MCAFEE: Okay. I still don't know how
9 useful it is at this point. Thank you.

10 DR. THOMAS: Dr. Hiatt?

11 DR. HIATT: Wow. That's obviously
12 comprehensive, as always. Would you care to comment
13 beyond the surrogate indices? You reviewed in detail
14 what you think the effect of extreme weight loss would
15 be on reducing the risk of cardiovascular events, fatal
16 and non-fatal. You made a comment there.

17 Can you also tell us what you think is
18 associated with those changes? What is it about weight
19 loss in particular that might be modifying risk?

20 DR. ECKEL: Well, it's interesting. If the
21 bariatric surgery approach is what you're going to
22 utilize to say that cardiovascular disease events and

1 potentially mortality, although not shown in SOS, is
2 benefitted, they looked at a number of covariates that
3 might have predicted the benefit.

4 Blood pressure, interestingly enough, was not
5 really reduced in SOS after major weight reduction from
6 bariatric surgery. And the reasons for that are a
7 little unclear, but I think, ultimately, the
8 hypertension issue is a chronic disease that
9 presumably, after years of uncontrolled hypertension,
10 or maybe even partially controlled hypertension, that
11 the arterial pathology really continues to exist and
12 the hypertension effect is not there.

13 But it seemed that the benefit did, in part,
14 relate to the changes in lipids and particularly in the
15 changes in glycemia. But anyway, I'm not sure we have
16 a total explanation for why there was a benefit.

17 DR. THOMAS: Dr. Yanovski?

18 DR. YANOVSKI: Bob, great talk, as always.
19 One of the things I know is implied by what you said is
20 that tachycardia, of course in and of itself, is
21 observed in obesity.

22 DR. ECKEL: Right.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

98

1 DR. YANOVSKI: Actually, tachycardia -- or at
2 least failure to drop heart rate has been one of the
3 signals for at least some of the drugs that have been
4 under development for obesity and was a cardinal sign,
5 I think, for sibutramine's effects.

6 Can you comment on how powerful heart rate is
7 as a predictor compared to some of the other things
8 you've discussed in regards to obesity?

9 DR. ECKEL: If you look at cross-sectional
10 data in terms of heart rate or simply just pulse,
11 ultimately there is a predictor for more negative
12 outcomes. But the question is, when you co-vary that
13 with many other factors, how relatively important is
14 it? And in fact, I kind of anticipated this question,
15 here and I did look this up to some extent. It's a
16 minor player in terms of the many things that co-vary
17 with heart rate.

18 But I think, in your considerations going
19 forward, ultimately heart rate is an issue, and I don't
20 think it can be dismissed. It's simply that heart rate
21 is a predictor, but a weaker one compared to many other
22 predictors of reduced mortality, or reduced longevity,

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

99

1 or early mortality.

2 DR. THOMAS: Dr. Bergman?

3 DR. BERGMAN: Bob, thanks for that wonderful
4 review. I have two questions. I guess they're both
5 about measurements. And one is the real role of
6 insulin resistance, because as I look at these trials,
7 insulin resistance is very rarely actually assessed.

8 DR. ECKEL: Correct.

9 DR. BERGMAN: The failure, the weakness of
10 the homer measure is not generally appreciated, but in
11 fact, what people are looking at is insulin. So is
12 insulin the problem, or is insulin resistance the
13 problem?

14 DR. ECKEL: You're entering into a lively
15 debate that's gone on now for 30 or 40 years. Is
16 insulin itself a cardiovascular disease risk factor?
17 As you point out, the ways to assess insulin resistance
18 in the population are crude and not very interpretable.
19 The homer IR is not a good measure of insulin
20 resistance.

21 So there are two schools of thought, that the
22 hyperinsulinemia we see in insulin resistance states is

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

100

1 simply compensatory. Ultimately, insulin needs to be
2 hyperproduced, ultimately to accommodate substrate
3 metabolism in a normal way. And the other idea is
4 insulin has effects as a mitogen in the arterial wall
5 and may enhance arterial smooth muscle cell
6 proliferation and other components of the vascular
7 wall. I'm not sure that that area has been
8 convincingly solved at this point. I have an opinion,
9 but I think it's still an active area of investigation.

10 DR. BERGMAN: The other issue relates to men
11 versus women. So in the first picture, you showed this
12 difference of BMI versus risk as a function of gender.
13 But for a given BMI, the actual percent adiposity in
14 men and women is quite different.

15 DR. ECKEL: It is.

16 DR. BERGMAN: So I wonder, if you had an
17 accurate measure of adiposity, would that difference go
18 away? Because I think that's another underappreciated
19 thing, that the BMI is quite different in terms of its
20 reflection on adiposity in men versus women.

21 DR. ECKEL: Richard, my take on the adiposity
22 issue for women is, I think, in general, particularly

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

101

1 in BMIs less than 30, that almost -- I shouldn't say
2 almost always, but many, many times that's lower
3 abdominal adiposity and not central adiposity.

4 I think as age increases and also BMIs get
5 above 30, we see more centralization of body fat, so
6 upper body obesity is more common. More visceral fat,
7 I think the risk increases there. So your comment is a
8 good one, but I think it relates to body fat
9 distribution.

10 DR. THOMAS: Dr. Alexander?

11 DR. ALEXANDER: Thanks for that fabulous
12 overview. I'm interested in the relationship between
13 weight loss and these various cardiovascular
14 improvements, and whether they vary by -- or whether we
15 know anything about whether the might vary by the
16 mechanism of weight loss, bariatric surgery --

17 DR. ECKEL: Right.

18 DR. ALEXANDER: -- diet and exercise, drugs,
19 the degree of weight loss, or the duration of weight
20 loss.

21 DR. ECKEL: Right. All good questions. I
22 think, in general, we think about this 5 percent level,

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

102

1 and that's somewhat mythical I think. In general, a 10
2 percent weight reduction will modify almost all of
3 these comorbid conditions that are associated with
4 obesity and cardiovascular disease risk.

5 The exception may be hypertension. Again, I
6 think that relates to the SOS study. I think people
7 with longstanding hypertension may not get permanent
8 improvement. The problem with a lot of these types of
9 assessments are people carrying out measurements of the
10 comorbidities during active weight reduction.

11 If you understand body weight, I think during
12 active weight loss and hypercaloric feeding,
13 ultimately, everything seems like it's falling. But
14 the question is, what about three months and past the
15 weight stability, after the weight reduction? And I
16 think that's important.

17 LDL is another one of those things. I didn't
18 talk at all about LDL today, but LDL always falls with
19 weight reduction except for an Atkins diet. And that's
20 because it's loaded with saturated fat. So LDL falls,
21 but if you measure LDL four to six weeks into dieting
22 and you're losing a pound a week, LDL is going to be

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

103

1 down. But the permanent effects are not there for LDL
2 cholesterol. So there's a perfect example where the
3 timing of the measurement relates to the benefit and
4 the comorbidities.

5 Let me close and say I think 10 percent
6 weight reduction modifies most, if not all, the co-
7 morbidities except perhaps blood pressure.

8 DR. THOMAS: Dr. Kaul?

9 DR. KAUL: Thank you. You talked about
10 factors that influence insulin sensitivity or
11 resistance, improved endothelial function, anti-
12 inflammatory effects, and triglyceride lowering. And
13 yet we have a class of compounds that are endowed with
14 all of these desirable attributes. And yet they are
15 labeled as recently updated because of a potential
16 increase in the risk of blood sugar, implying that they
17 might be diabetogenic.

18 So where does this paradigm fall apart?

19 DR. ECKEL: Sanjay, good question. So I
20 think there are a couple members of this panel who
21 ultimately have recently written about the issue of the
22 fibrates story in patients who were not

1 hypertriglyceridemic. We're begging the right
2 triglyceride-lowering trial to ultimately assess
3 whether it's beneficial or not.

4 So with the fibrate issue in ACCORD, I think
5 we dismissed that trial as uninformative because of the
6 experimental design. To statins in diabetes risk, I'm
7 on ATP-4, and I can assure you, we are carefully
8 considering the statin risk for type 2 diabetes. And I
9 can't tell you what the panel will say. That report is
10 being begged by many and will be out this calendar
11 year, I can assure. And if Denise Simons-Morton were
12 here, she would agree to that.

13 All that aside, I think the statin risk, if
14 you look at the data, is modest compared to the benefit
15 of a patient with type 2 diabetes or at risk for
16 cardiovascular disease with impaired glucose tolerance.
17 It appears that the risk is far more reduced with the
18 statin therapy other than the risk of developing type 2
19 diabetes. That's my comment on that issue.

20 DR. KAUL: I have one more question. Did I
21 hear you correctly when you said that the SOS 15-year
22 follow-up did not show a mortality reduction,

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

105

1 cardiovascular mortality reduction?

2 DR. ECKEL: I think it was events only, not
3 cardiovascular mortality.

4 DR. KAUL: I thought it was the reduction in
5 cardiovascular deaths, about 50 percent. And when you
6 look at the total cardiovascular events, the p value is
7 not significant. And when you adjust it for variables,
8 I think they achieved statistical significance. This
9 is the JAMA paper, published in January of this year.

10 DR. ECKEL: Correct. And I know the paper
11 well, but you may be correct. I may have
12 misinterpreted that in terms of events versus
13 mortality. I thought it was mortality, not affected
14 events, but you may be correct. I'll need to just
15 clarify that. Thank you.

16 DR. THOMAS: Dr. Proschan?

17 DR. PROSCHAN: Yes. You mentioned, in
18 response to Dr. Yanovski's question, that the heart
19 rate was not really that important of a predictor. And
20 I'm just wondering, does that hold for -- I mean, it
21 seems to me that it might be different if you
22 artificially increase heart rate with, say, a diet drug

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

106

1 in someone who's obese. Is that still, do you think,
2 not a very big predictor?

3 DR. ECKEL: Eric, I know, is going to be
4 speaking about the SCOUT trial this afternoon. And the
5 question exists as to whether the increase in pulse
6 and/or blood pressure related to the outcome in SCOUT.
7 And I think, at this time, an increase in heart rate
8 does need consideration in terms of the potential risk.
9 I really, at this point in time, can't relate to that
10 trial in terms of speaking to whether it was pulse,
11 blood pressure, or both that related to the outcome.
12 But perhaps Dr. Colman will this afternoon.

13 DR. THOMAS: Dr. Hendricks?

14 DR. HENDRICKS: You mentioned sudden cardiac
15 death. I wonder if you could expand a little bit on
16 that.

17 DR. ECKEL: Presumably, that relates to
18 cardiac arrhythmias. I think it's been poorly studied.
19 I know sudden cardiac death is a tough problem to
20 investigate. The idea may relate to some of the other
21 electrocardiographic abnormalities we see in patients
22 with obesity that might predispose them to sudden

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

107

1 cardiac death. This tends to occur with more severe
2 obesity and less so in patients with BMIs between 30
3 and 35.

4 DR. THOMAS: Dr. Capuzzi?

5 DR. CAPUZZI: Yes. I just wondered if you
6 would comment on within the metabolic syndrome, the
7 changes, the increased risk imparted on by changes in
8 LDL particle concentration, and the modifications of
9 LDL in that situation.

10 DR. ECKEL: Another controversial question.
11 How important is LDL particle size or LDL density in
12 cardiovascular disease risk? I would contend that most
13 of that work comes from the laboratory and not from
14 human studies. And if you'd look at the many
15 covariates that relate LDL size to outcomes, it's
16 trumped by most every other thing.

17 Currently, I think the lipid field in general
18 feels that measuring LDL subfractionation by
19 sophisticated methodologies such as the VAP, or AnaMar
20 technology, or the Berkeley HeartLab, does not add
21 anything to the management of the lipid patient.

22 So I think it's controversial whether small,

1 dense LDL is particularly athrogenic. And clearly, in
2 patients with obesity, you're going to see more of it,
3 but if look at patients with hypertriglyceridemia, 90
4 percent of people with triglycerides above 200 have
5 small, dense LDL.

6 DR. CAPUZZI: I guess my point is, how can
7 you separate out the risk imparted by individual
8 factors that comprise that? For example, the small
9 dense LDL increase is part of it. Hypertriglyceridemia
10 is part of it. Hypercoagulation is part of it.
11 Modification in the artery wall and the other
12 lipoproteins.

13 Can you really separate those all out in
14 terms of which element is imparting more risk, or can
15 you not?

16 DR. ECKEL: No. I don't think you can
17 because they're so highly associated. I mean, you can
18 look at one clinical trial or other, how they're
19 modeled in terms of assessing the outcome, the relative
20 independence, or interrelationships between variables.
21 It's tough to really accurately sort out all these
22 things that hang out in the insulin resistance

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

109

1 paradigm.

2 DR. CAPUZZI: Thank you.

3 DR. THOMAS: Dr. Seely?

4 DR. SEELY: I wanted to get back to your
5 comment about increase in pulse. So increase in pulse
6 is a common signal of a number of the weight loss
7 drugs. And increase in pulse may be associated with
8 maintenance of heart rate variability or it may be seen
9 with a decrease in heart rate variability. So the
10 increase in pulse may come from -- be associated with
11 different mechanisms --

12 DR. ECKEL: Sure.

13 DR. SEELY: -- which may then have different
14 prognostic values.

15 So in studies that are being mandated to
16 enroll such a large number of individuals, do you have
17 a suggestion about looking at the relationship of
18 increase in heart rate with heart rate variability and
19 how to apply that to such large populations?

20 DR. ECKEL: You cardiologists in the crowd
21 may be able to answer this better than me, but with
22 increasing heart rate in obesity, there appears to be

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

110

1 less heart rate variability.

2 So the question comes up when you're
3 considering pharmaceuticals that may modify heart rate.
4 I think the thing that needs to be considered is, is
5 that an average increase that reflects the
6 distribution? Is that distribution skewed? What can
7 we learn from the sibutramine experience to say who
8 might be at risk and who's not at risk?

9 I don't have much wisdom here in terms of how
10 to assess this heart rate variability. Again, I think
11 the relatively independent contribution of heart rate
12 is modest compared to many of the covariates that hang
13 out with it.

14 DR. THOMAS: Are there any other questions of
15 the panel? I just would like to remind everyone, Dr.
16 Eckel will not be here tomorrow. So if you do have
17 questions, this is the best time to ask. And we will
18 have some additional time later today.

19 Since no one else seems to have a question or
20 they're thinking about it, I have a question for you,
21 Dr. Eckel.

22 As you mentioned, the changes in weight loss

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

111

1 are overemphasized during the weight loss period, but
2 are different in the maintenance period. So when would
3 you recommend -- if you're going to do an analysis of
4 efficacy on these surrogate markers, what time would
5 you want to do that analysis? So for example, the
6 guidance says to look at one year, but maybe the weight
7 loss is at six months, and then you're maintaining that
8 for six months. But it may be a continuous weight loss
9 for a year in some drugs.

10 So would you want to do the maintenance
11 evaluation for efficacy at a two- or three-month period
12 after you see a plateau?

13 DR. ECKEL: It's a complicated question,
14 Abraham. I think the question, as I understand it
15 best, is at what intervals would I assess biomarkers
16 during an active and persistent weight loss program?

17 Is that kind of summarial?

18 DR. THOMAS: Yes.

19 DR. ECKEL: So I feel that in someone who's
20 losing minimal amounts of weight and ultimately or
21 actively losing weight, that measurements of biomarkers
22 during that interval is unnecessary and not very

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

112

1 informative. So I want to see at least a 5 percent
2 weight loss in my patients before I assess anything,
3 and I want a period of weight stability.

4 In much of my research that has looked at
5 reduced obesity and metabolic factors that are improved
6 by weight reduction, I've allowed three months of
7 weight stability before I do anything metabolically.
8 And that's because if we look at insulin sensitivity
9 immediately after weight loss, it's modestly improved
10 compared to what was before weight reduction. But if
11 we look at it three months later, it's much, much
12 improved.

13 So there is this temporal sequence. And so
14 the three-month interval is not well proven. It could
15 be six weeks. But at that point, I would measure, once
16 weight stability has been reached on a medication,
17 after bariatric surgery, or simply by lifestyle
18 modification, weight stability, and then three months
19 of weight stability, and then we'd measure biomarkers.
20 Then I would do it every six months subsequent to that,
21 to assure that the weight loss and the biomarkers are
22 both favorably modified.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

113

1 DR. THOMAS: Dr. Goldfine?

2 DR. GOLDFINE: Dr. Eckel, I'm going to expand
3 on that question. I'm sorry. I'm going to ask you
4 with my back to you.

5 In clinical practice, when patients are
6 actually losing weight via lifestyle, dietary, and
7 exercising interventions, extraordinarily modest weight
8 loss can be associated with quite favorable effects on
9 these biomarkers, such that even, you know, a pound of
10 month that could be continued over long term might be
11 more favorable than a 10-pound loss and drop.

12 From your previous comments, can you try to
13 expand whether or not you think that, if you were doing
14 this by pharmacological intervention about the rate of
15 weight loss and the stability, how you would interpret
16 it from drug-assisted changes?

17 DR. ECKEL: Dr. Goldfine, I think that your
18 question is a very appropriate one, based on my
19 previous comment. There are patients who want to know
20 things during active weight loss. And as a physician,
21 I'm kind of flexible there if somebody really wants to
22 know something. But I want to make sure he or she

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

114

1 interprets the data correctly in terms of where they're
2 at in the weight loss paradigm.

3 Now, back to drugs. If a patient is
4 receiving a pharmaceutical for weight reduction -- and
5 by the way, I happen to use a fair amount of
6 phentermine. This is just me. I use phentermine in
7 only people that eat because they're hungry because in
8 my anecdotal experience, people that don't eat from a
9 hunger-motivated drive do not respond to the drug.

10 I'm currently carrying out a protocol to
11 assess this objectively, but my history of 10 or 15
12 year of using appetite suppressants, ultimately, the
13 people that respond are people that are hungry. And if
14 you're a grazer and have no hunger-motivated food
15 intake, there's no response.

16 So that's kind of a rabbit trail. Let me
17 come back.

18 So if a patient requests measurements during
19 active weight loss, I might give into that and measure
20 them, but a patient on a drug, particularly something
21 that might be a new player in the pharmaceutical arena,
22 I maybe would obviously turn to the FDA, and package

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

115

1 inserts, and things like that to assess things more
2 regularly. I'm not sure I answered your question.

3 DR. GOLDFINE: Well, I think that if we're
4 thinking about developing drugs, that they may have
5 different rates of weight loss over the course of the
6 year. And so for recommending the frequency of the
7 monitoring of these, does that mean that we shouldn't
8 interpret anything if a drug has a slow, progressive
9 weight loss as opposed to a rapid drop and then a
10 stability? So when you actually start doing these
11 measurements and how we should be interpreting them is
12 actually very important.

13 DR. ECKEL: Well, that said, if you look at
14 weight loss drugs historically or if you look at
15 lifestyle intervention for weight loss, almost all the
16 weight's off by six months. People plateau at that
17 point. It's unusual to see someone after six months
18 have additional weight reduction. Now, that doesn't
19 mean it couldn't occur.

20 So I think, unless some of the drugs you're
21 going to be considering have a longer phase of weight
22 reduction, then obviously my answer would be modified

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

116

1 accordingly.

2 DR. THOMAS: Thank you, Dr. Eckel.

3 We will now take a 15-minute break. Panel
4 members, please remember that there should be no
5 discussion of the meeting topic during the break,
6 amongst yourselves, or with any member of the audience.
7 We will resume at 10:30 a.m.

8 I just want to put in a reminder for panel
9 members, if they're going to take lunch today, that
10 they should remember to pay at the food area,
11 concession stand outside. You might want to do that
12 now as opposed to before lunch.

13 (Whereupon, a recess was taken.)

14 DR. THOMAS: We will now proceed with our
15 presentation from Dr. Bill Knowler. I'd like to remind
16 public observers at this meeting that while this
17 meeting is open for public observation, public
18 attendees may not participate except at the specific
19 request of the panel. I'd also like everyone to note
20 that there will be a slight change in today's agenda.
21 Dr. Wing will be presenting before the noon lunch hour,
22 and Dr. Bray will be presenting after lunch, which is a

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

117

1 change from the original schedule.

2 Dr. Knowler?

3 DR. KNOWLER: Yes. Good morning. I'm going
4 to talk to you this morning about obesity and type 2
5 diabetes. And as indicated here, I am from the
6 National Institute of Diabetes and Digestive and Kidney
7 Diseases in Phoenix.

8 For many years in Phoenix, I've worked with
9 American Indian populations in the southwest. And this
10 slide is some data published a number of years ago,
11 which I think is very good to introduce the topic of
12 obesity and type 2 diabetes. This shows on the Y axis
13 the incidence rates of diabetes, new cases developing
14 over time in, adult Pima Indians, according to body
15 mass index, measured when people were non-diabetic. So
16 this is longitudinal data, not cross-sectional data.

17 As you can see, we have a very powerful
18 relationship of body mass index with the incidence of
19 diabetes being extremely low in the very thin to very
20 high in the highest BMI categories, no evidence of a
21 threshold at which the risk begins.

22 Data such as this really led to the question,

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

118

1 what happens if we have non-diabetic adults who have a
2 very high body mass index? If we can help those people
3 lose weight to get in a lower category, will their risk
4 of developing type 2 diabetes also go down, as
5 suggested by this slide?

6 Data such as this led to the Diabetes
7 Prevention Program, or DPP, which is a multicentered,
8 randomized clinical trial conducted in the United
9 States, testing the hypothesis that type 2 diabetes can
10 be prevented or at least delayed by treating modifiable
11 risk factors, obesity being one of the primary ones.

12 We selected persons who are at high risk of
13 developing type 2 diabetes, but did not have the
14 disease. And this study was carried out from 1996 to
15 2001, and it was followed with a long-term follow-up
16 study, which is now still in progress, and that's
17 called the DPP Outcomes Study.

18 These are the eligibility criteria for people
19 enrolled in the study. They were adults at least 25
20 years of age, although the mean age at entry was 51
21 years. They had elevations of both fasting, plasma
22 glucose, and 2-hour plasma glucose. So these are

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

119

1 roughly equivalent of what we now call impaired fasting
2 glucose and impaired glucose tolerance, so they're
3 elevated but not meeting criteria for the diagnosis of
4 diabetes.

5 They had a body mass index of at least 24
6 kilograms per meters squared. We wanted people who had
7 a high enough BMI that there was room for weight loss,
8 although again, the mean body mass index in these
9 people was over 30, so they were clearly obese. The
10 primary outcome of the study was development of
11 diabetes, which was assessed by fasting plasma glucose,
12 measured every six months, or an oral glucose tolerance
13 test assessed annually.

14 Once we had determined patients who were
15 eligible, they were randomized into three treatment
16 groups. All three groups got standard diet and
17 physical activity advice that we would give to people
18 who already had diabetes. But in addition, they were
19 randomized to one of three groups. Two of these groups
20 were a double-blind drug comparison, comparing placebo
21 with metformin. And the third group was not blinded.
22 It was a lifestyle intervention group. They received

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

120

1 no drug or placebo, but an intensive lifestyle
2 intervention, which we abbreviate ILS. And as you can
3 see, there were a little over 1,000 people in each of
4 these three groups for a total study size of 3,234.

5 I'm now going to show you results from the
6 first phase of DPP, again, which went until 2001. This
7 shows the mean weight changes. The intensive lifestyle
8 was aimed at achieving a goal of at least 7 percent
9 weight loss using standard behavioral techniques, that
10 is, attention to diet, specifically fat calorie
11 reduction, and modest physical activity.

12 As we've heard before and many people are
13 familiar with, with the behavioral weight loss program,
14 we saw the maximal weight loss at 6 to 12 months and
15 then a gradual regain of about half of that weight loss
16 over the next few years.

17 The placebo group, shown in green, on average
18 was remarkably stable, very little weight change over
19 this time period. And the metformin group, while
20 receiving exactly the same behavioral advice as the
21 placebo group, because this was a double-blind
22 comparison, did lose about 2 kilograms. This is also

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

121

1 equivalent to about 2 percent of body weight, which was
2 fairly well maintained over an -- this was average of
3 three years, but because of a staggered enrollment
4 period ranged from about two to four years. So we're
5 showing some data up to four years at this point.

6 Now, the primary outcome of this study was
7 not weight loss, but was development of diabetes. Ad
8 that's shown in this life table figure here, where the
9 placebo group is shown in green, which has the highest
10 rates, then the metformin group, and the lifestyle
11 intervention group.

12 The reason these lines have the stair-step
13 function is because of the annual assessments with the
14 glucose tolerance test. A few people developed
15 diabetes and were clinically diagnosed because of
16 symptoms in between the annual examinations, but
17 because of the frequent follow-up of these people,
18 almost all were diagnosed by research tests, and that
19 leads to this stair-step cumulative incidence rate.

20 The differences between all these groups were
21 very highly significant, as shown up here. And in
22 fact, these results were so dramatic that the data and

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

122

1 safety monitoring board, which of course was unmasked
2 to the study results, recommended early termination of
3 the study at this point, which was a recommendation
4 that the institute took.

5 These rates are shown in a different way
6 here, which is a little bit simpler for comparison I
7 think. The annual diabetes incidence rates in the three
8 treatment groups is shown on the Y axes in number of
9 cases per 100-person years of observation. In the
10 placebo group, the rate was 11 per 100-person years;
11 that is, on average, 11 percent of the people in the
12 placebo group each year, who had remained non-diabetic,
13 developed diabetes during the subsequent year. And
14 this was actually quite close to what we had predicted
15 based on the literature that people with these criteria
16 would have in the absence of treatment.

17 Metformin reduced that rate to 7.8 per 100
18 per year or a 31 percent reduction, and the intensive
19 lifestyle decreased the rate even more by 58 percent.
20 So this was really a dramatic result and one that
21 surprised many of us, that the intensive lifestyle was
22 so effective and more effective than the drug

1 intervention.

2 The DPP enrolled or tried to enroll a lot of
3 the minority groups in the United States that are at
4 highest risk of developing diabetes. These are the
5 numbers in the five groups that were enrolled in this
6 study. And as you know, in the population as a whole,
7 there are big ethnic differences in risks of type 2
8 diabetes, with rates being much higher in American
9 Indians, Hispanics, and African Americans than in the
10 white population.

11 In this particular study, if you look at the
12 placebo group, they're receiving only standard diet and
13 exercise advice. The rates were uniformly high.
14 There's no significant difference among the ethnic
15 groups. So the selection criteria we had for selecting
16 high-risk groups managed to select people who are at
17 high risk, and those risk factors really overcame the
18 ethnic differences that are seen in the population
19 data.

20 The metformin, again, was equally effective
21 in all of the groups. There are no differences among
22 the ethnic groups in the rate reduction due to

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

124

1 metformin or due to lifestyle, shown in blue. So these
2 treatments, both metformin and the intensive lifestyle,
3 not only were effective, but were uniform effective
4 according to ethnic groups in the study, also in both
5 sexes, which I'm not showing here in detail.

6 Why do we think this lifestyle worked so
7 well? I know we're talking about drugs here, but I have
8 to emphasize the effectiveness of the lifestyle
9 intervention in DPP. Weight loss was really the key.
10 Although we did encourage people to do activities, it
11 was the weight loss that really made the difference.
12 We attained that by very conventional methods, getting
13 people to reduce total calories, and we focused on fat
14 reduction.

15 I know there's a lot of controversy as to
16 what diets are best for weight reduction. We did not
17 study that question. We used one approach. This is
18 what we used and this is how it worked. And then also
19 achieving 150 minutes of moderate activity, such as
20 brisk walking, each week seemed to be what led to this
21 lifestyle success.

22 So here's an example of the weight loss. I

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

125

1 showed the weight loss curve, the average weight loss
2 of 7 percent or so after a year. That, of course, was
3 an average. There was a large variation among people.
4 And we modeled the average weight loss during the three
5 years of the DPP and the estimated risk of diabetes,
6 according to that weight loss. And that modeling is
7 shown here, that the greater the weight loss, the
8 greater the hazard rate of developing diabetes.

9 So remember, in the placebo group, the hazard
10 rate was about 11, which is equivalent to the people in
11 the ILS group who actually didn't lose any weight. Or
12 if they were in the group and didn't lose weight, it
13 didn't reduce their diabetes incidence. The more
14 weight they lost, the greater the reduction in risk.
15 So we really think it was the weight loss, not just
16 participation in a program which led to the risk
17 reduction.

18 We did a somewhat similar analysis, comparing
19 the metformin and placebo group. I showed you that
20 metformin led to a modest weight loss. It also led to
21 a 31 percent reduction in diabetes incidence rate. So
22 we tried to ask the question, was that risk reduction

1 due to the weight loss or due to other actions of
2 metformin? It's certainly very difficult or impossible
3 to tease this out for certain, but in terms of modeling
4 drug action and weight loss in their combination, we
5 came up with this figure.

6 So in the placebo group, there is also
7 variation in weight. Some gained weight. Some lost
8 weight. On average, there was no weight change. But
9 the model indicates that those who gained weight in the
10 placebo group actually had a higher risk of diabetes.
11 Those who lost weight had a lower risk.

12 We had a similar pattern in metformin,
13 although the slope was smaller. And for a given rate
14 change, the risk was lower in metformin than in the
15 placebo group. So in the metformin treatment, weight
16 loss explained a lot of the effect, but certainly not
17 all of it.

18 So I would like to emphasize again, since
19 we're talking about drugs and obesity, in my mind,
20 metformin should be considered as a weight loss drug,
21 as well as a drug for treating and preventing diabetes.

22 We have looked at other factors which might

1 influence the effects of the Diabetes Prevention
2 Program interventions. Specifically, we've started
3 looking at genetic effects. And the first one that we
4 were able to look at was a gene called TCF7L2, which,
5 at this time in 2006, had recently been discovered in
6 Europeans to be a strong diabetes-susceptibility gene,
7 according to cross-sectional case control studies.

8 We evaluated this in the DPP, looking at the
9 placebo group, which received minimal intervention. We
10 saw that those who are homozygous for the T allele,
11 which had previously been reported to be associated
12 with type 2 diabetes, had about an 80 percent higher
13 risk of diabetes than those in the other two genotypes.

14 If the people were treated with metformin,
15 the risk was lowered overall, but especially in those
16 with a high-risk genotype. The lifestyle treatment
17 resulted in the lowest incidence of diabetes
18 altogether, the greatest benefit in those with the
19 high-risk genotype. In fact, the lifestyle
20 intervention obliterated the genotypic effect that had
21 been seen in other studies and seen in the placebo
22 group.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

128

1 So the encouraging message here is, although
2 genotypes in many cases will influence someone's risk
3 of disease, having a high-risk genotype, at least for
4 type 2 diabetes, doesn't mean that that person will
5 inevitably get the disease. It actually meant, in this
6 case, that they may actually derive more benefit from
7 an intervention than someone with a lower risk
8 genotype. And this is just the beginning of a field of
9 trying to see to what extent genetic information can
10 help guide treatment for disease prevention or
11 treatment.

12 There were many other benefits of the DPP
13 lifestyle intervention and, to some extent, the
14 metformin intervention on cardiovascular risk factors.
15 I don't have the time to go through all this, so a lot
16 of data are just summarized in this one slide.

17 These have been published in a series of
18 three different articles, all published in 2005 on the
19 journals listed here, but basically, the lifestyle
20 intervention improved a large number of cardiovascular
21 risk factors. And again, metformin had generally lesser
22 improvements, but improvements in most of these as

1 well.

2 But in terms of the question that's on
3 people's minds today, what about cardiovascular
4 disease, we had, at this time, too few cardiovascular
5 disease events to evaluate for a treatment effect. And
6 I'll get to the follow-up in a minute, but we have
7 still not reported cardiovascular disease events in the
8 DPP or in its follow-up study.

9 So when we had this premature termination of
10 the planned DPP in 2001, we decided on the advice of
11 the data and safety monitoring board, and the
12 institute, et cetera, that we would make a transition
13 into a follow-up study, which is called the DPP
14 Outcomes Study. This started in 2002 and is now
15 planned to continue through
16 2014.

17 We ended the masked phase of the placebo
18 metformin because of the dramatic effects of metformin.
19 We elected to continue treating with metformin in an
20 unmasked, open-label phase for those originally
21 assigned to it. We discontinued the placebo. And we
22 offered all subjects, regardless of initial group, the

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

130

1 lifestyle intervention, since that had been shown to be
2 definitely the preferred intervention in this group.

3 The goal of this is, now, we're looking at
4 the long-term effects of the DPP interventions on long-
5 term weight loss maintenance, further incidence of
6 diabetes in those who hadn't developed diabetes in the
7 first three years, and diabetes complications, and
8 mortality.

9 This shows the longer-term effects now of the
10 interventions on weight loss. This is with a median of
11 10 years of follow-up since randomization and this was
12 published about two and a half years ago. This is very
13 similar to the three-year curve I showed you before.
14 The placebo group has remained remarkably stable,
15 although an indication of a little bit of weight loss
16 in the last couple of years.

17 The lifestyle intervention, which had this
18 peak weight loss at 6 to 12 months and the gradual
19 regain. The regain now has plateaued, so they regained
20 most of the weight loss, but they did not continue
21 regaining up to baseline. So they have stabilized at
22 about a 2 and a half percent weight loss, which now

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

131

1 appears to be well maintained for 10 years. And the
2 metformin group that lost weight during the first year
3 has been remarkably stable for a long time.

4 So I believe, although this weight loss for
5 metformin was very modest, I'm not aware of any other
6 data from either drug or lifestyle weight loss studies
7 that have this remarkable long-term weight loss effect.
8 I might add that this is with a very complete follow-
9 up. Generally over 90 percent of study visits are kept
10 in DPP and DPPOS.

11 What has this done to diabetes incidence?
12 This is the life table curve now I showed you before.
13 About the first three years looked like this. Now, the
14 rates have tended to flatten out and become parallel
15 among all three groups. The rate of new development of
16 diabetes has actually slowed down in the placebo and
17 metformin groups, compared to what it was in the first
18 three years. And the lifestyle group has flattened out
19 a little bit at the end, but the difference that was
20 attained early has been largely maintained over time.

21 Notice, though, that over 10 years, although
22 there still are remarkable treatment effects, if you

1 look at things in an absolute sense, we can't say that
2 we still know how to prevent diabetes because, still,
3 close to half of the people who enrolled in the trial
4 have developed diabetes over a 10-year period. But at
5 least it's been substantially delayed in those who have
6 had the interventions.

7 Getting back to weight loss, though, I showed
8 you this upper left-hand figure a minute ago. That's
9 looking at all ages in the study. We've also divided
10 this up according to three age groups. And these are
11 ages at randomization, so people are now 10 years older
12 in the 10-year age groups.

13 This is the middle group and this is the
14 older group at randomization. You can see that the
15 general treatment patterns are the same in all of
16 these, but overall, the effects of weight are
17 different. I think just following what typically
18 happens in adulthood with weight, the younger group,
19 there's a tendency in the placebo group, especially, to
20 actually gain weight over time.

21 The lifestyle group has, on average,
22 completely regained their baseline weight. The middle

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

133

1 group sort of patterns what we see overall. And in the
2 oldest group, we see weight loss on average in all
3 groups, although still greatest in the metformin and
4 the lifestyle intervention groups.

5 So what about effects on vascular disease,
6 which, again, is an important topic for this meeting
7 today. The micro- and macrovascular outcomes that
8 we're anxiously awaiting in the DPPOS, unfortunately I
9 can't tell you anything about that yet. We are
10 expecting to conclude that evaluation and report these
11 results in about two years.

12 We did recently just publish a paper, in
13 fact, just last week on cost effectiveness, a cost
14 study of treatment and medical costs in the DPP and
15 DPPOS, looking at the whole 10-year experience. Shown
16 in sort of small numbers here on this scale are
17 estimates of the costs of actually providing the
18 intervention.

19 These costs, of course, are always very
20 difficult to estimate, where it's not the whole cost of
21 the program. We tried to separate the costs of
22 actually providing the advice, the follow-up, et

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

134

1 cetera, from the specific research costs, the costs of
2 collecting data, et cetera. So this is our estimate of
3 the treatment costs. And not surprisingly, it was
4 lowest in the placebo group, intermediate in metformin,
5 and highest in the lifestyle group because of the
6 intensive personnel activities creating the lifestyle
7 intervention.

8 But then we estimated costs of medical care
9 outside the study, so this would include
10 hospitalizations, doctor visits, medicines, et cetera,
11 that people had, and this is cumulative over the 10
12 years of the study. And the placebo group had the
13 highest cost, metformin was in the middle, and the
14 lifestyle group was actually the lowest. So in terms
15 of outside medical care, these interventions looked
16 like they were saving money.

17 If you just add the two up together, you get
18 the green bars, which is a little bit hard to see the
19 differences here, because of this scale. So if we
20 really want to focus on this area here, where we can
21 look at these scales, I'll truncate the access and
22 redraw this here, where we now have a scale from

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

135

1 24,0 to \$30,000.

2 Again, you see what it showed before. The
3 outside medical care costs were highest in placebo,
4 lowest in lifestyle, intermediate in metformin. And
5 when you add the treatment costs within DPP, you can
6 see that, according to these estimates, metformin
7 actually would save money over a 10-year period. Not
8 only would it prevent diabetes and improve many
9 cardiovascular risk factors, but actually saves money
10 to the healthcare system, according to these estimates.

11 The lifestyle intervention cost a little bit
12 of money, but it was estimated that, per quality-
13 adjusted life-year, the lifestyle intervention cost
14 approximately \$10,000 per quality, which I'm not a
15 health economist myself, but I understand is at the low
16 range of most things we do in medicine to try to
17 improve people's health. There are very few cost-
18 saving things, immunizations being one of them, but
19 perhaps metformin for diabetes prevention could also be
20 put in that category.

21 I now want to switch and show data. There
22 have been several other studies looking at diabetes

1 prevention in high-risk people. And I'm just picking
2 on one, and I'm picking on it because this shows some
3 topics that we have been talking about already this
4 morning.

5 This was a study of orlistat, one of the
6 approved weight loss drugs. This was a study, a four-
7 year study, one of the few long-term studies, looking
8 at weight loss in a placebo group and a group given
9 orlistat, so showing greater weight loss in orlistat.
10 And the goal was to see if they could have an effect on
11 diabetes, and that's shown here, the life table
12 incidence of diabetes in the placebo group and in the
13 orlistat group being much lower.

14 But in contrast to the DPP, the big problem
15 with this study, as with some of the others we heard
16 about already this morning, is that very few people
17 completed the study going out four years, only about
18 half of those in orlistat and only 34 percent in
19 placebo.

20 In my opinion, studies like this cannot be
21 interpreted. I don't think there is any statistical
22 method that can be used to extrapolate data to a time

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

137

1 period when you haven't collected data. And there is
2 certainly the worry that in weight loss studies, those
3 people who are not losing weight or who have lost
4 weight and start regaining will become frustrated and
5 will not come back in to be weighed. We don't know
6 that. If we had those data, we wouldn't have this
7 problem.

8 But so many studies like this, where the
9 people drop out, my own view is, a study like this
10 can't be interpreted at all. You can't infer data
11 beyond where you've measured data, in my opinion.

12 I will mention, though, that there have been
13 several other clinical trials similar to the DPP that
14 have had similar results and that I think have had
15 outstanding follow-up. So the idea that lifestyle
16 intervention in particular will prevent or delay type 2
17 diabetes, I think is beyond a doubt right now. As I
18 showed, it doesn't do enough. Still, a lot of people
19 get diabetes, but it clearly has a major effect.

20 Unfortunately, there is still little evidence
21 for long-term non-glycemic outcomes. And what I mean
22 by this is, are we simply preventing someone's blood

1 sugar from crossing an arbitrary diagnostic level and
2 getting a disease label? Or are we actually preventing
3 people from getting the disease manifestations which
4 actually bother people, like retinopathy, kidney
5 disease, heart disease, strokes?

6 Unfortunately, there is very little data on
7 this. There is a Chinese study -- which was one of the
8 first in this series, so they have longer-term follow-
9 up -- that's reported an effect of a lifestyle
10 intervention on development of retinopathy. All of
11 these studies, including that one and the DPP, are
12 collecting data on complications, mortality, et cetera.
13 And so I think we'll have answers to these questions
14 soon, but so far, little of this has been published.

15 Lastly, I would like to shift gears
16 altogether and talk about early life predictors of
17 obesity and diabetes. I am going to show some data
18 from the Pima Indian longitudinal study I've been
19 working with in Arizona for many years. The reason I'm
20 changing gears and showing this is that all the studies
21 we've seen so far, what we've been talking about, have
22 been studies in obese adults, often older adults. And

1 I believe that if we're really going to solve the
2 problems of obesity and diseases related to obesity,
3 that we're starting the game way too late. And so I
4 just want to talk to you a little bit and try to
5 convince you that the problem really does start very
6 early on.

7 So again, I'm going back a number of decades
8 to some data we published years ago from the
9 longitudinal study in the Pima Indians. These are the
10 kind of data that can only come from a longitudinal
11 population study. They are intergenerational and they
12 require many years of follow-up.

13 We classified pregnant women, as to during
14 pregnancy, whether they had diabetes during that
15 pregnancy, which in most cases preceded the pregnancy,
16 or whether at that time they were pre-diabetic or
17 remained non-diabetic. Now, we're using the word "pre-
18 diabetic" not in its current use, but in its proper
19 English use, meaning the time before diabetes.

20 So these are women who actually had normal
21 glucose tolerance during the pregnancy, but sometime
22 later in their life, because they were in a

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

140

1 longitudinal study, developed diabetes. So they were
2 pre-diabetic. They had genetic susceptibility factors
3 for diabetes. They ultimately developed diabetes,
4 whereas the women shown in dark blue were non-diabetic
5 and remained non-diabetic throughout follow-up, in
6 many cases for many decades.

7 So what we see here is that the offspring of
8 the diabetic mothers had a higher birth weight. This
9 is using some old indices that we don't use anymore.
10 The absolute values don't matter. It's just that these
11 people were about 20 percent heavier on average than
12 the offspring of the pre-diabetic or diabetic mothers.
13 And these two groups didn't differ by each other. The
14 scales differed at different age groups. They were
15 looked at with different references, but the basic
16 pattern remained. On average, the offspring of the
17 diabetic mothers were heavy at birth. They stayed
18 heavy throughout childhood. They became obese
19 adolescents.

20 There was very little difference between the
21 offspring of the diabetic and the non-diabetic mothers.
22 And we inferred from this, or we hypothesized from

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

141

1 this, that there was likely something in the exposure
2 to diabetes in utero that set up these kids to be
3 destined towards obesity, and not only obesity, but
4 diabetes, shown in the same definition of groups here,
5 non- diabetic, pre-diabetic, and diabetic.

6 The offspring of the diabetic pregnancies
7 started developing diabetes early in life. And this is
8 all type 2 diabetes. Type 1 diabetes has not been
9 clearly documented to exist in full heritage American
10 Indian populations. So this is type 2 diabetes
11 occurring very early. When we get into the older ages,
12 it's starting to occur in the offspring of non-diabetic
13 pregnancies. But it's predominantly a problem in early
14 ages of being an offspring of a diabetic pregnancy.

15 So to deal with obesity and diabetes at young
16 ages, at least in this population, we really have to
17 back things up a generation, and we have to manage or
18 prevent diabetes in pregnant mothers.

19 This obesity in childhood is very important.
20 This is looking at relative weight in tertiles, again,
21 weight relative to height and age and sex, very
22 strongly predictive of the subsequent development of

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

142

1 diabetes, as strong as measures of their insulin or
2 glucose are.

3 So these observations have led to what we've
4 called the vicious cycle hypothesis, where you have a
5 woman who has diabetes. Obviously, she gives rise to
6 an infant of a diabetic mother, and the short-term
7 complications of that have been well-known for decades.
8 But what we've found is that if that infant is a
9 daughter, she is very likely to grow up to be a young
10 woman with type 2 diabetes and to develop diabetes
11 before she becomes pregnant or at least before she
12 finishes all her pregnancy. Thus, she will become a
13 pregnant woman with diabetes, perpetuating this cycle.
14 And this cycle has actually led to a dramatically
15 increasing prevalence of type 2 diabetes in children in
16 this population.

17 So ultimately, I think at least in these
18 high- risk populations, such as American Indians, we
19 need to break this cycle. And I'm happy to say that
20 there are clinical trials being started right now to
21 address this very problem.

22 So in conclusion, overweight, obesity,

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

143

1 however you want to define them, are strongly related
2 to the risk of type 2 diabetes. We've seen in the DPP
3 that metformin and lifestyle interventions in adults
4 can reduce weight. They can reduce the incidence of
5 diabetes. Our recent paper suggests that you can even
6 reduce healthcare costs. Whether they will reduce the
7 incidence of diabetes complications and cardiovascular
8 disease is still an open question.

9 Early life conditions influence obesity and
10 diabetes. And ultimately, I think we need to start
11 very early or even in the mothers, before kids are
12 born. And we've also seen from some of the studies
13 I've shown, and many others we've heard about earlier
14 today, that there are many ways to reduce body weight.
15 I've shown you we can do it with lifestyle
16 intervention, or metformin, with or without drugs.
17 Maintenance of that body weight loss, of course, is
18 very difficult.

19 When you have many possible treatment
20 approaches, there are many ways to treat obesity. It
21 reminds me of a statement from one of my famous
22 playwrights from over 100 years ago, who really hit the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

144

1 nail on the head. "If many cures are offered for an
2 illness, you may be sure that the illness has no cure."

3 So I hate to end on that pessimistic note and
4 hope that we can eventually come up with better ways to
5 cure this illness and its associated morbidities.

6 DR. THOMAS: Thank you for your excellent
7 presentation, Dr. Knowler.

8 Dr. Iyasu, could you introduce yourself for
9 the record?

10 DR. IYASU: My name is Solomon Iyasu. I'm
11 the director of the epidemiology division at the FDA,
12 Office of Surveillance and Epidemiology.

13 DR. THOMAS: We'll now have our next speaker,
14 Dr. Rena Wing.

15 DR. WING: We changed the order because we
16 felt it was very appropriate for the Look AHEAD trial
17 to be following from the DPP trial because that's
18 actually what happened in history. The success of the
19 DPP I think really led to the development of the Look
20 AHEAD trial, which I'll be discussing.

21 I'm going to try first to give you a
22 rationale and design of the Look AHEAD trial. Then

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

145

1 I'll talk to you about the year 4 results in terms of
2 changes in weight and fitness, and then finally the
3 year 4 results in terms of changes in cardiovascular
4 disease risk factors.

5 So Look AHEAD is a multicenter, randomized
6 clinical trial examining the long-term effects, up to
7 13 and a half years, of an intensive lifestyle
8 intervention program on cardiovascular morbidity and
9 mortality in over 5,000 overweight or obese persons
10 with type 2 diabetes. It's funded by the NIH primarily,
11 with institutes shown here, with also co-funding from
12 the CDC.

13 Now, it's well-known that weight loss is
14 recommended for individuals with type 2 diabetes and
15 that's because there have been many studies showing the
16 short-term benefits of weight loss for these
17 individuals. In the short term, if you have an
18 individual with diabetes treated with weight loss,
19 they'll show improvements in their lipids, their blood
20 pressure, their insulin sensitivity, and their glycemic
21 control.

22 However, in contrast, there have actually

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

146

1 been no randomized trials to determine the long-term
2 consequences of intentional weight loss. Surgical
3 studies, which typically are not randomized, suggest
4 positive effects of very large weight losses, such as
5 the SOS study. However, observational studies have
6 suggested that weight loss and weight cycling may
7 actually be associated with increased morbidity and
8 mortality. Now, in observational studies, we don't
9 know often if the person is ill and, therefore, losing
10 weight because of their illness. So clearly, you need
11 randomized trials to try to disentangle this, but there
12 really have been no major randomized trials assessing
13 this.

14 Hence, NIH decided to fund the Look AHEAD
15 trial. And as I pointed out in the beginning, I want to
16 emphasize a few aspects of Look AHEAD. It's a
17 multicenter trial examining the long-term effects of an
18 intensive lifestyle intervention. The program is
19 designed to produce both weight loss and increases in
20 physical activity. And we're looking at the outcomes
21 of cardiovascular morbidity and mortality. And this
22 study is being conducted in individuals with type 2

1 diabetes.

2 These individuals have been randomized to one
3 of two arms, an intensive lifestyle intervention or
4 diabetes support and education, which is our control
5 group. And the primary hypothesis is that the
6 intensive intervention, compared to DSE, will reduce
7 the incidence rate of an aggregate endpoint of CVD,
8 defined as cardiovascular death, non-fatal MI, non-
9 fatal stroke, and hospitalization for angina over 13.5
10 years of follow-up.

11 We have several secondary outcomes that are,
12 again, composites. So our secondary outcome is the
13 first composite, is CVD death, non-fatal MI, non-fatal
14 stroke. The next composite includes all-cause death,
15 non-fatal MI, non-fatal stroke, and hospitalization for
16 angina. And the third composite includes many of the
17 same, plus at the end, hospitalizations for congestive
18 heart failure, coronary CABG, or angioplasty, carotid
19 endarterectomy, and peripheral vascular disease. All
20 are added to those outcome measures.

21 Look AHEAD is also looking at other outcomes,
22 including cardiovascular disease risk factors, diabetes

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

148

1 control and complications, general health and
2 hospitalizations, quality of life and psychosocial
3 outcomes, and costs, and cost effectiveness.

4 To enter the Look AHEAD trial, individuals
5 had to have type 2 diabetes. They had to be
6 overweight, with a BMI greater than 25 or greater than
7 27 if they were on insulin, aged 45 to 75. We were
8 hoping to achieve at least 33 percent minority. We
9 could have people with or without CVD. They had to
10 have controlled blood pressure, controlled hemoglobin
11 A1, less than 11 percent, triglycerides less than 600.
12 And we wanted less than 30 percent using insulin
13 because we were concerned that insulin might make it
14 more difficult to lose weight.

15 This slide shows the baseline characteristics
16 of individuals who actually entered the trial. As you
17 can see, about 60 percent were women; 37 percent were
18 minorities. On average, we were at 59 years of age.
19 Sixteen percent were insulin users, BMI of 36, weight
20 of 100 kilograms, and 15 percent had a history of a
21 prior CVD event.

22 Now, I want to emphasize to you that this was

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

149

1 an intensive lifestyle intervention and has been kept
2 ongoing throughout the entire Look AHEAD trial. So at
3 the beginning of the study, people came in weekly for
4 six months. Then they came in three times per month
5 for the next six months. And then they've been coming
6 in two times per month from year 2 to the end of the
7 trial.

8 The program includes group plus individual
9 sessions, so we use a combination because we think
10 there is strengths to both group and individual. And
11 the program focuses on diet, physical activity, and
12 behavioral strategies, so it's intensive in all those
13 ways.

14 We recommend that individuals lose 10 percent
15 of their body weight and then try to maintain it. We
16 do this by placing them on a calorie and fat-restricted
17 diet. And we've actually used meal replacements and
18 structured menus to help people adhere to these dietary
19 goals. The physical activity is to gradually increase
20 minutes of brisk walking, moving up to a goal of 175
21 minutes per week, and we also give pedometers and
22 encourage people to reach 10,000 steps per day. The

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

150

1 diabetes support and education group, as I say, is our
2 control group, and they attended three to four meetings
3 per year, primarily to promote retention.

4 One of the important things in Look AHEAD is
5 that we made a decision that the medication adjustments
6 for participants should be made by their own physician.
7 The only place where Look AHEAD investigators adjusted
8 medication was during the very early weeks of the
9 intensive lifestyle intervention, where we adjusted
10 diabetes medications in order to prevent hypoglycemic
11 reactions, as people rapidly lost weight at the
12 beginning.

13 Look AHEAD was designed to have 90 percent
14 power to detect an 18 percent reduction in CVD risk
15 over 10 and a half years of follow-up. Looking at
16 different observational, epidemiological studies, we
17 developed an assumption of what the rate of
18 cardiovascular disease event rate would be in our
19 population. And we estimated that we would have 3.125
20 percent CVD event rates per year in the control group.

21 Actually, when we started the study and we're
22 looking at our control group, our DSMB pointed out to

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

151

1 us that we better be careful because we were not
2 achieving what we had assumed was not occurring in the
3 control group. And in fact, in the control group,
4 there was only a 0.7 percent CVD event rate.

5 We are totally blinded to the event rate
6 overall or to the event rate in the intensive lifestyle
7 intervention arm, but we were told that we were low on
8 our CVD event rate for our control group. So we
9 convened an endpoint working group that was masked to
10 the study results, except for the knowledge of the
11 control group, and asked to think about this and
12 consider whether we should make an alteration in our
13 outcome measures at this time.

14 They first considered why we have the low
15 event rate in Look AHEAD. One possibility, highly
16 likely, is that there have been secular trends in the
17 use of medications for CVD risk factors. A second is
18 that the trial participants are typically healthier
19 than observational cohort studies. We thought we had
20 adjusted for that, but we probably didn't adjust
21 enough.

22 The other thing is that we required, in Look

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

152

1 AHEAD for safety, that all participants have a graded
2 exercise test and pass that test prior to starting the
3 Look AHEAD study. We found that of those people who
4 took a graded exercise test, 11 percent did not meet
5 our safety criteria and thus did not enter the trial.
6 So our graded exercise test may have excluded those
7 people at greatest risk for having a CVD event soon in
8 the study. So that's an important thing to think about.

9 Now, having considered those causes for the
10 changes in our control group, this endpoint working
11 group carefully thought about what should be the
12 solutions. And by the way, I want to really encourage
13 you to look at this paper by Brancati on clinical
14 trials that discusses this whole issue of changes in
15 our study design, but also the broader issue of changes
16 in clinical trial studies.

17 But based on their deliberations, what was
18 decided was that we should extend the study duration by
19 two years and that we should broaden the definition of
20 the primary endpoint to include hospitalized angina.
21 So originally, our primary hypothesis included only
22 what was shown here in white. We added to our primary

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

153

1 hypothesis, as shown here in yellow, hospitalizations
2 for angina, and we extended our follow-up from 11 and a
3 half to 13 and a half years, and have proceeded
4 according to this new primary hypothesis.

5 Now, I want to turn to the year 4 results. I
6 should point out that at this point in time in Look
7 AHEAD, our patients are just about finishing their year
8 8 study visits. However, we've only analyzed and
9 published results through year 4, and that's what I'm
10 showing you today.

11 One of the points I'd like to make is that at
12 year 4, we are continuing to follow 94 percent of the
13 randomized participants and 96 or 97 percent of those
14 participants who are still alive. So we have lost
15 some, unfortunately, due to death. But I want you to
16 see the types of follow-up rates that occur in the
17 Diabetes Prevention Program and that are being seen in
18 Look AHEAD. We are following 95 percent of our
19 participants at year
20 4.

21 These show the weight changes in these
22 participants. In the red line are the weight changes

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

154

1 in the control group. The blue line are the changes in
2 the intensive lifestyle intervention. And as has been
3 pointed out before, we achieved our maximum weight loss
4 at one year. Even though these were diabetics and we
5 thought we'd have less success at weight loss than in
6 the Diabetes Prevention Program, we actually had better
7 weight losses, achieving close to a 9 percent weight
8 loss or 8.5 kilogram weight loss. There has been some
9 gradual regain over the next several years, but it
10 looks like between years 3 and 4, there's been a
11 plateauing in the regain, with participants maintaining
12 almost a 5 percent weight loss in the intensive
13 lifestyle intervention arm.

14 Now, I also am showing you the changes in the
15 control and the intervention arm in terms of the
16 percent of participants meeting certain criteria that
17 one might say are successful. Somebody might say,
18 well, if they've lost any weight not gained over the
19 baseline, it's a success.

20 If you use that criterion, 74 percent of the
21 ILI participants have been successful at year 4,
22 clearly more than in DSE. If you use the criterion of

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

155

1 having lost at least 5 percent of your body weight, 46
2 percent of participants in ILI are successful at year 4
3 compared to 25 percent in DSE. And if you take an even
4 stricter criteria of saying having lost at least 10
5 percent, we have 23 percent of our participants in ILI
6 compared to 10 percent in the control group.

7 We also achieved and maintained significant
8 improvements in fitness levels. We did maximum stress
9 tests at the beginning and then some max tests at year
10 1 and 4. And as you can see here, the intensive
11 lifestyle intervention group had approximately a 20
12 percent change in their fitness levels in baseline to
13 one year, and if maintained, almost a 10 percent
14 improvement compared to baseline at year 4.

15 Now, we found no evidence that gender
16 affected the weight loss, not significant differences
17 between men and women in Look AHEAD. And we also found
18 no evidence at year 4 of differences between insulin
19 users and non- insulin users. That was actually a
20 surprise to us. We also, in contrast to many who
21 believe that lifestyle interventions are not
22 appropriate for severely obese individuals, actually

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

156

1 showed that severely obese individuals do quite well in
2 the Look AHEAD trial.

3 So this divides the intensive lifestyle
4 intervention participants into four groups according to
5 their initial BMI. So we have the overweight group,
6 the class I, II, and severe obese groups. And as you
7 can see here, all four groups had comparable weight
8 losses -- actually, I shouldn't say that. The
9 overweight group had the lowest weight losses in terms
10 of percent changes in body weight. But the severely
11 obese did just as well as class I and II obese
12 individuals. So I think this goes against the mantra
13 that you shouldn't be using lifestyle intervention for
14 severely obese individuals. They actually performed
15 quite well in our program.

16 At year 4, we found no significant
17 differences in weight loss across the various
18 race/ethnicity groups in our trial. And like the DPP,
19 we found once again that the oldest participants in our
20 intensive lifestyle intervention group lost more weight
21 than those who were younger in our lifestyle
22 intervention group.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

157

1 We then looked to see why are the older
2 individuals losing more weight, and we find that it's
3 very related to their better adherence. The older
4 individuals attended more sessions during the first
5 year. They attended more sessions between years 2 and
6 4. They actually report doing more physical activity
7 at year 4 than the younger age groups, and they report
8 eating less at year 4. So if you eat less, and you
9 exercise more, and you come to a lot of sessions,
10 you're going to have better weight losses, and that's
11 exactly what we see.

12 Now, I'd like also to just show you the four-
13 year trajectories of the 887 intensive lifestyle
14 participants who lost more than 10 percent of their
15 weight loss at year 1. We're now looking at what
16 happens to those people over the next three years. And
17 there's a small number of them who regain it all, only
18 10 percent.

19 In contrast, 42 percent of those individuals
20 who lost more than 10 percent at four years are still
21 maintaining a 10 percent weight loss. There's 17
22 percent who haven't maintained it in full, but are

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

158

1 still between 7 and 10 percent. And there's another 11
2 percent who have maintained at least greater than the 5
3 percent weight loss. And then there's 20 who have
4 regained the majority of what they lost.

5 In the next few slides, what I want to show
6 you is differences in adherence across those different
7 weight loss categories. So these are all people who
8 lost 10 percent at year 1, and I'm basing my adherence
9 data on what happens to them between years 1 and 4.

10 So the group of people who lost more than 10
11 percent at year 1 and are still down 10 percent at year
12 4 are the ones shown to your left. And you can see
13 that those individuals attended, on average, 24
14 meetings over years 2 to 4 of the program, and they
15 attended more than those individuals who regained more
16 of their weight or who had gained weight compared to
17 their year 1.

18 We also find that those individuals who lose
19 10 percent and stay in the lost greater than 10 percent
20 use more meal replacement products and they report
21 higher physical activity levels, quite a bit higher,
22 than all the groups who regain weight over time. So

1 again suggesting that this difference in what happens
2 between years 1 and year 4 is due primarily to
3 adherence to the treatment program.

4 We look at the variables associated with
5 percent weight loss at year 4. We find that baseline
6 characteristics explain only a small percent of the
7 variance, treatment attendance, about 4 percent of the
8 variance, dietary intake or physical activity, another
9 2 percent, approximately. But the year 1 weight loss
10 is the strongest predictor of the year 4 weight loss.
11 So if you lose weight initially, you are likely to also
12 be successful long term. If you do very poorly
13 initially, you are likely to do very poorly long term.
14 And that's been shown in many different trials, but is
15 shown here. And, as I say, is the biggest driver of what
16 happens at year 4.

17 So in terms of weight loss, the conclusions
18 would be that the ILI produced significantly greater
19 changes in weight and fitness through four years.
20 Nearly 50 percent maintained a loss greater than 5
21 percent. The intervention produced clinically
22 significant weight losses in all subsets of a diverse

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

160

1 population, and the best predictors related to
2 adherence and initial weight loss.

3 Now, I'd like to turn to the changes in CVD
4 risk factors. So looking first at hemoglobin A1c, you
5 can see that the intensive lifestyle intervention,
6 which again is shown in blue, had the greatest benefit
7 for hemoglobin A1 during year 1. There was then some
8 return to baseline in hemoglobin A1, but even at year
9 4, individuals in the intensive group have maintained a
10 better improvement in their hemoglobin A1 from baseline
11 compared to the control group.

12 Now, this slide I just want to walk you
13 through for a minute because I'm going to use this
14 format in others of my slides. This looks at the use
15 of diabetes medications over the course of Look AHEAD.
16 It starts off on the left with those people who are not
17 using any diabetes medication at baseline. You can see
18 there's only about 350 in each arm. And within that
19 group, it looks at how many had to start using a
20 diabetes medication over time. And you can see that
21 many more in DSE started using -- a larger percentage
22 started using a medication compared to ILI.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

161

1 Over on the right-hand side, it looks at
2 those people who were using a diabetes medication and
3 looks at what percentage had to stay on that
4 medication. And you can see that many more in ILI, 9
5 percent in ILI, by the end of it were still off of a
6 diabetes medication, compared to only 4 percent in DSE.
7 So at each of the years, more people in DSE had to
8 start on medication, and fewer were able to come off of
9 their diabetes medications. The same pattern is shown
10 here with insulin. You can see more in DSE starting on
11 insulin. And of those who were using insulin at the
12 beginning, fewer stopping using insulin in DSE.

13 This slide shows the prevalence of achieving
14 the ADA goal for hemoglobin A1c. The goal is to be
15 less than 7 percent. You can see, at the beginning of
16 the study, about 45 percent of both groups were. And
17 then in all four years, significantly more of the ILI
18 group had achieved that goal than the DSE, so many more
19 in ILI. They have better improvements in their
20 hemoglobin A1, they need less medication, and they're
21 more likely to achieve the ADA goal.

22 Systolic blood pressure shows a similar

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

162

1 pattern, greatest improvements at year 1, but
2 maintenance of the improvements through year 4.
3 Diastolic blood pressure, however, shows a different
4 pattern, where we had significant differences between
5 the two arms at year 1, but by year 3 and 4, there are
6 no longer significant differences between the two arms.

7 The changes in medication sort of parallel
8 that with significant differences during the early
9 years with the intensive lifestyle intervention needing
10 and using less medication, but by the end, by years 3
11 and 4, the two groups being quite comparable.

12 The percent achieving the ADA goal is similar
13 in the sense that the first few years, we saw benefits
14 of ILI. And by year 3, it's going away, and in year 4,
15 it's no longer statistically significant.

16 This looks at HDL cholesterol. This is
17 actually one of the outcome measures that is most
18 positive in the Look AHEAD trial. We show significant
19 improvements in HDL cholesterol in the ILI, relative to
20 the DSE, at all four years with pretty much a
21 consistent benefit through all four years, so no
22 diminution of the effect over the four years of the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

163

1 trial.

2 LDL cholesterol is the only variable where we
3 actually show greater improvements in the diabetes
4 support and education group than the ILI. So look at
5 this slide carefully. The improvements here are
6 greater in DSE than in ILI. So we wondered why. And
7 we looked carefully at the use of lipid medications.
8 And again, look at this slide on the left side; about
9 1300 in each arm not using lipid medications at the
10 beginning of the study. Many more in DSE. For example
11 at year 1, 25 percent of those individuals not using it
12 had been started on lipid medications, typically
13 statins, compared to 18 percent in ILI.

14 In every year of the trial, more of the non-
15 baseline users have been started on lipid medications.
16 And by the way, I want you to note, at the end, at four
17 years, 50 percent of those individuals not using these
18 medications had been started on them. It's a major
19 thing that I think you, thinking about FDA studies,
20 have to think about, is the use of medication and what
21 it's doing to your outcome measures for CVD. And among
22 those who were using lipid medications at baseline,

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

164

1 almost nobody in either arm stops using them. So
2 you're into this secular trend of the increased use of
3 lipid medication.

4 If I adjust for lipid medications, and I go
5 back and I look at my LDL cholesterol, I now see that,
6 if anything, basically all the effects are no longer
7 statistically significant. Across all four years,
8 they're not different, and at none of the four years is
9 there a difference between ILI and DSE. So one of the
10 important points here is the effect and the confound
11 due to medication changes on your CVD risk factors in
12 these types of trials.

13 This looks at the prevalence of achieving a
14 goal for LDL cholesterol. And as you can see here,
15 there were no differences until year 4, where, if
16 anything, there's more in the DSE than in ILI, and
17 that's due to more people using the statins.

18 One point I'd like to make for you all is
19 just to look within the Look AHEAD study at the changes
20 in risk factors that occur in relation to the magnitude
21 of weight loss. So I'm going to show you how weight
22 losses of just 5 to 10 percent can produce significant

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

165

1 improvements in each of the CVD risk factors except for
2 LDL cholesterol.

3 Now, this series of slides I'm showing you is
4 done only at year 1. I haven't done these analyses yet
5 for year 4. But at year 1, here are the changes in
6 hemoglobin A1c. And you can see -- I mean, if you
7 can't read them at the bottom, the group over to the
8 left is gained weight, gained greater than 2 percent.
9 The next bar is gained 2 percent or lost 2 percent, so
10 that's basically your stable group. The next one is
11 lost 2 -- less than 5 percent. And all three of those
12 groups basically have no changes in hemoglobin A1c. If
13 you lose 5 to 10 percent of your body weight, you have
14 about a .5 percent reduction in hemoglobin A1c, clearly
15 greater if you lose 10 to 15 percent, and clearly
16 greater if you lose greater than 15 percent. So very
17 strong relationship for hemoglobin A1c.

18 The same is true for blood pressure. Shown
19 at the top here is diastolic blood pressure. At the
20 bottom is systolic blood pressure. And you can see,
21 especially for systolic blood pressure, a very strong
22 relationship between the magnitude of weight loss and

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

166

1 the improvements in blood pressure. But actually, it's
2 there for both.

3 Here's HDL cholesterol on the top, shown once
4 again, very nice relationship between the amount of
5 weight you lose and the improvements in HDL
6 cholesterol. And down below is LDL cholesterol. We
7 show in Look AHEAD absolutely no relationship between
8 magnitude of weight losses and improvements in LDL
9 cholesterol. So if you go back to those other slides I
10 was showing you on ILI/DSE, the differences between the
11 two groups in LDL seems to be primarily due to use of
12 statins. Weight loss in our study is not having any
13 effect on LDL cholesterol.

14 So in conclusion, ILI has produced sustained
15 improvements in glycemic control, systolic blood
16 pressure and HDL cholesterol, as compared to the DSE.
17 LDL cholesterol improved more in DSE than in ILI due
18 primarily to increased statin use. After adjusting for
19 the medication use, changes in LDL didn't differ. And
20 modest weight losses improved all the CVD risk factors
21 with the exception of LDL cholesterol.

22 I think there are just a few take-home

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

167

1 implications for the FDA and you all to think about in
2 your deliberations. One is that intensive lifestyle
3 interventions, if they're intensive and if they're
4 ongoing, can produce sustained benefits for weight and
5 for fitness across diverse age, gender, ethnic, racial
6 groups, and weight categories.

7 Initial weight losses and adherence to the
8 program are consistently the strongest predictors of
9 long-term weight loss. Modest weight losses can
10 produce sustained improvements in glycemic control,
11 systolic blood pressure, and HDL cholesterol.

12 One of the things, as I've tried to emphasize
13 in my presentation, is that you all are going to have
14 to think about how changes in medication fit into these
15 analyses of changes in CVD risk factors or changes in
16 cardiovascular disease events. The other thing that I
17 think Look AHEAD emphasizes to you is that it is
18 possible to retain participants, high percentages of
19 participants, in long-term weight loss trials. In
20 lifestyle interventions, we consider not even
21 publishing our results if we don't maintain at least 80
22 percent of our participants through at least several

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

168

1 years of follow-up. So I think that standard really has
2 to be thought about in terms of drug trials for weight
3 loss.

4 Finally, Look AHEAD is going to continue to
5 follow our participants to determine the long-term
6 impact of intensive lifestyle intervention on CVD
7 morbidity and mortality. We won't know that outcome
8 until 2014. Thank you.

9 DR. THOMAS: Thank you, Dr. Wing, for your
10 excellent presentation.

11 We'll now take questions for both Dr. Wing
12 and Dr. Knowler.

13 Dr. Brittain?

14 DR. BRITTAIN: Yes. This is for Dr. Wing.
15 Again, my question is for you. Yes. Again, just to
16 follow up on the great follow-up that you had and are
17 achieving in your study. Since that's so important,
18 can you attribute that to anything? I'm wondering if
19 it's linked to the relationship you have by having this
20 lifestyle intervention, if that's related to that.

21 DR. WING: Let me point out that our
22 retention is excellent also in our control group. And

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

169

1 in many trials, actually, even though everyone says,
2 "If you have a control group, you can have much more
3 problems with retention," actually, in most studies you
4 actually find that retention is better in the control
5 group, I think because they are less embarrassed if
6 they haven't lost weight.

7 But I was thinking about this during the
8 earlier presentations. One of the things in the
9 diabetes prevention program, Look AHEAD, is that we
10 provide honorariums to participants for attending
11 annual visits. In Look AHEAD, to be specific, we
12 provide \$100 honorarium each time, each annual visit.
13 We describe it as, it's covering their costs, that they
14 had to travel to the clinic. They had to take time off
15 from work, et cetera. So that's why it's called an
16 honorarium. But I think those types of honoraria can
17 be very important in getting participants who have not
18 lost weight or are not coming, attending the meetings,
19 to return at least for your annual visits, your key
20 outcome measures. I think there is also the
21 development of a rapport with both arms of the study,
22 not only the intensive lifestyle, but also the control

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

170

1 group in these large trials.

2 DR. THOMAS: Dr. Hiatt?

3 DR. HIATT: A couple of quick questions. In
4 DPP, what was the effect of metformin on weight loss in
5 those who developed diabetes compared with those who
6 did not? Was it equally effective?

7 DR. KNOWLER: We haven't analyzed that. You
8 mean specifically on those after they developed
9 diabetes? We haven't looked at that yet.

10 DR. HIATT: Was the weight loss effect
11 sustained in those who converted to diabetes?

12 DR. KNOWLER: No. I can't answer that.

13 DR. HIATT: In Look AHEAD, what was the
14 effect of weight loss on heart rate?

15 DR. WING: I'm sorry?

16 DR. HIATT: What was the effect of weight
17 loss on heart rate?

18 DR. WING: Heart rate? We have not looked at
19 that.

20 DR. HIATT: In Look AHEAD, have you done a
21 way to integrate all these changes in cardiac risk
22 factors as an integrated Framingham risk kind of

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

171

1 assessment?

2 DR. WING: We have stayed away from that,
3 based on concerns about unblinding ourselves and
4 revealing too much of the data to ourselves about how
5 the trial is going. So we have a list of things that
6 we are not allowing ourselves to look at yet. And one
7 of them is a Framingham risk score. So we have not put
8 them together.

9 The heart rate question, by the way, I could
10 answer for you very simply, but I don't know it off the
11 top of my head.

12 DR. HIATT: So you think that looking at the
13 individual components won't unblind you, but somehow
14 putting it all together would?

15 DR. WING: That was the decision that the
16 steering committee made.

17 DR. HIATT: Okay.

18 DR. THOMAS: Dr. Waters?

19 DR. WATERS: Going back to the adherence
20 question, I think it's really amazing that in the
21 earlier drug trials that Dr. Golden talked about, we're
22 talking about 50 percent adherence in one year. And

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

172

1 you're both 90 percent over 10 years. And I agree with
2 you that paying somebody \$100 for a follow-up helps a
3 little bit, but that doesn't keep them exercising twice
4 a month or doing all of the other things.

5 I wonder if you'd both like to comment on
6 maybe you're looking at a different type of patient
7 that's someone who signs up for a study where they're
8 going to take a pill that's going to fix all their
9 problems is not the same as someone who's signing up
10 for a 10-year study, where they're going to have to do
11 all those sorts of things that you tell them about up
12 front.

13 Are they really just different patients?

14 DR. WING: I'd like to answer you in two
15 ways. First of all, I want -- you implied that because
16 I'm following 95 percent, that that means 95 percent
17 are still doing the physical activity. That is not
18 necessarily true. In other words, 95 percent are
19 coming to the visits, but clearly, many of them are not
20 adhering to the diet and exercise prescription. I wish
21 95 percent were still exercising.

22 DR. WATERS: But a lot still are?

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

173

1 DR. WING: Many are, but clearly, that's not
2 the equivalent of the 95 percent. Okay? Whether we're
3 admitting different types of participants, I really
4 don't know because we thought that might be an issue on
5 the DPP, where we were trying to get participants who
6 were willing to come into both types of programs.

7 But I don't know, and your point is well
8 taken, that that could be part of it, that people
9 coming in wanting a medication may want a quick fix.
10 But also, my own history of doing drug trials has been
11 that I've had very good retention in drug trials. I
12 haven't done them in 20 years. I've done very few.
13 But I think you can bring some of the techniques from
14 lifestyle intervention to retention in drug trials.

15 DR. KNOWLER: I'd like to comment also. I
16 think, although this is very hard to quantify -- I
17 mean, I think the reason that both Look AHEAD and DPP
18 have been so successful in retaining participants is
19 that we put a great emphasis on participant/staff
20 interactions. Regardless of what group they're in, we
21 really try to get to know the participants. We have
22 social events with the participants that are totally

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

174

1 unrelated to the treatment. And I think, for both
2 studies, we just have incredibly dedicated staff who
3 are looking out for the participants' best interests
4 and the participants feel that and feel devoted to the
5 staff as well.

6 DR. RASMUSSEN: So I have a couple of
7 questions. So one is relating to --

8 DR. THOMAS: Actually --

9 DR. RASMUSSEN: I'm sorry. I thought I was -
10 -

11 DR. THOMAS: No. Dr. Proschan?

12 DR. PROSCHAN: Yes. I don't know if you have
13 this information, but this is for Dr. Wing. You
14 mentioned a low control rate, which is a problem with
15 trying to interpret whether weight loss by medication
16 has any -- we're going to have to deal with that with
17 respect to losing weight by medication use. And I'm
18 wondering if you have information on how the control
19 rate -- how much it increased when you added the
20 hospitalized angina.

21 Then I also just wanted to make a comment
22 about the retention rate. I think, if Dr. Wing can get

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

175

1 94 percent retention by four years, then I think this
2 committee should insist on at least 90 percent
3 retention after one year. How does she do it?

4 Maybe all the drug companies that are getting
5 these new drugs should talk to Dr. Wing, because she's
6 getting it done.

7 (Laughter.)

8 DR. WING: Let me just answer a couple of
9 your questions. I thought of another thing that we do
10 in lifestyle interventions, typically. We have what we
11 call a run-in, and I think many of the drug trials do
12 too, where we say to the person, "This is what's going
13 to be involved in this study. You are going to have to
14 keep a diary of what you're eating and your exercise.
15 So I don't care. You don't have to figure out calories
16 in it or anything, but keep the diary and see what it's
17 like." And if they come back -- they have to do that
18 for two weeks, typically.

19 If they come back after two weeks and they
20 say, "This was horrible. I'm not willing to do this,"
21 then we don't randomize them. We also meet with them
22 and interview them. And if they say, "I'm in in the

1 middle of a terrible divorce, and I'm caring for my
2 elderly mother, and there's no way I'm going to be able
3 to come to all these meetings," We don't randomize
4 them.

5 So those decisions are made up front with the
6 idea that these are efficacy trials, not effectiveness
7 trials, so that we are trying to select a group of
8 participants appropriate for efficacy trials, which
9 should be true in your drug trials as well.

10 Back to your second question about the event
11 rate. The expectation was that adding the hospitalized
12 angina would about double our event rate. And so that
13 was a partial solution. The lengthening of the trial
14 was a partial solution. And altogether, that plus the
15 aging of the population and what we expect will be
16 increasing rates over time, we are hopeful.

17 DR. THOMAS: Ms. McAfee?

18 MS. MCAFEE: I have two quick questions. One
19 is, Rena, I recall going to a scientific presentation
20 at the NIH when DPP was stopped. And several people in
21 the audience, myself included, were quite concerned
22 because your lifestyle program did not separate the

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

177

1 effect of weight loss, from diet composition, from
2 exercise. And I know there was talk about secondary
3 studies to look at that.

4 Was that done? I noticed slide 36 in your
5 presentation. Is that an attempt to do that? I'm just
6 not clear.

7 DR. WING: Do you want a comment on it from
8 DPP? Because that's where it was done.

9 DR. KNOWLER: Slide 36 in the DPP
10 presentation?

11 DR. WING: Yes, the DPP one.

12 MS. MCAFEE: No. I'm sorry. In Rena's
13 presentation.

14 DR. KNOWLER: In Rena's presentation.

15 DR. WING: In my presentation, it has not
16 been done yet. But in DPP, it was done. So in DPP, we
17 looked very carefully at was it the weight loss, was it
18 the change in fat, or was it -- I'll come back to this
19 slide. This is a little different point.

20 But the other is, in DPP, we really did look
21 at what was the component that was driving the
22 reduction in risk. And it was the weight loss that

1 drove the reduction in risk. Physical activity and
2 changes in dietary fat contributed to the weight loss,
3 but it was the weight loss that drove the reduction in
4 risk.

5 MS. MCAFEE: So there wasn't that much of a
6 component of exercise and diet composition that were
7 really helpful in this?

8 DR. KNOWLER: I'd like to comment on that,
9 too. I agree with what Rena said. And in fact, I
10 showed you a slide that the risk reduction was very
11 strongly related to the weight loss.

12 So when you try to tease out all the
13 components, the weight loss was important. The various
14 measures of dietary composition and physical activity
15 were not. But doesn't this sound a little
16 contradictory? I mean, how do you get weight loss?
17 You get weight loss by changing diet and physical
18 activity. The problem is, diet and physical activity
19 are very difficult to measure. We have very crude
20 measures. Weight loss, we can measure very accurately.

21 So what you can measure very accurately
22 turned out to be very important. The question that we

1 can't answer is -- and we didn't set out to answer:
2 what's the most effective way to get weight loss?

3 We didn't design this, you know, as a low-fat
4 diet compared to a low-carbohydrate diet, compared to
5 an exercise-only study. That's the kind of study that
6 needs to be done, and is being done to some extent, to
7 find out weight loss. That wasn't our goal. Our goal
8 was, if you get weight loss, does that reduce the
9 incidence of diabetes? That's the question we
10 addressed.

11 MS. MCAFEE: Then just real quickly, I
12 noticed -- and you talked about it in your presentation
13 I might have missed this slide, but you talked about,
14 there is a regain to about 2 and a half percent only of
15 lost weight.

16 Is there maintenance -- do their numbers,
17 their indicators, stay as good as they were at 5
18 percent? I'm not clear. I'm sure you've addressed
19 this, and I just missed it.

20 DR. WING: If you looked at all the changes
21 that I was showing you, for example, on systolic blood
22 pressure or hemoglobin A1c, all of them had that same

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

180

1 regain type of thing where they were drifting back
2 towards baseline in relationship to the regain of
3 weight, probably.

4 MS. MCAFEE: But when they got to the 2 and a
5 half percent, were their numbers still as good? Was
6 their Alc, cholesterol, was that still as good?

7 DR. WING: No.

8 MS. MCAFEE: Do we need a 5 percent weight
9 loss? Is 2 and a half percent going to do it?

10 DR. WING: I haven't looked at the
11 categorical data in terms of losing 0 to 5 percent, 5
12 to 10 percent at year 4 yet. We've only looked at that
13 at year 1 now.

14 I want to come back just for one minute to
15 the question of what produces weight loss. And I would
16 differ a little bit on whether we need more trials of
17 this. I would argue that we've had a lot of trials on
18 what produces weight loss, and that it's very clear
19 that the combination of diet plus exercise is better
20 than diet or exercise alone for long-term maintenance
21 of weight loss, that that combination is the best.

22 I would also argue that there have been

1 enough trials looking at the macronutrient composition
2 that suggest that it isn't the macronutrient
3 composition. It's more the total caloric restriction
4 and basically adherence to the diet.

5 So if you follow any diet and you reduce your
6 calories, you will lose weight better than any other
7 diet if you don't reduce your calories. Those are the
8 two things. So I think restricting calories, which
9 means adhering to the diet, and being physically active
10 are the two things I think are related to weight loss
11 and weight loss maintenance, particularly.

12 DR. THOMAS: Dr. Kaul?

13 DR. KAUL: Yes. My question is for Dr. Wing.
14 Was there any pathophysiologic rationale for choosing
15 hospitalization for angina to broaden your endpoint?

16 The reason why I'm asking this question is,
17 yes, you may capture more events, but you had a whole
18 menu of other secondary endpoints that you could have
19 chosen. And yet you chose hospitalization for angina,
20 which is, in my opinion, a rather subjective endpoint.
21 And if there is variability in the ascertainment of a
22 subjective endpoint, it's going to bias the results

1 towards the null.

2 Now, you're not interested in capturing more
3 events.

4 DR. WING: No, no.

5 DR. KAUL: You're interested in capturing the
6 contrast between the two treatment --

7 DR. WING: You're exactly right. You're
8 exactly right. And we very carefully considered it.
9 In fact, I brought it with me, the copy of the paper
10 that I alluded to about clinical trials that discusses
11 this in detail. I'd be happy to share it with you.

12 But hospitalized angina was felt to be one
13 that we could ascertain without bias because it was
14 hospitalized angina, not chronic, ongoing angina. And
15 we considered all of the other types of endpoints. We
16 felt that adding angina made the most sense. I mean,
17 we actually considered things like, should we add
18 cancer? Should we add all-cause mortality?

19 We really considered a group of different
20 things to think about. We felt that angina fit with,
21 first of all, our original intent in our primary
22 hypothesis, and also felt -- it seemed to fit to us

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

183

1 with where the field of cardiovascular disease was
2 going and where other clinical trials were going.

3 So in our decision, we had invited many
4 people from NHLBI and other cardiologists to help us
5 reach this decision, keeping them all blinded to the
6 outcomes as to what would be best to add as another
7 measure. And hospitalized angina was selected.

8 DR. KAUL: Let me just submit to you a
9 typical scenario. If I get called in to admit a
10 patient or to evaluate a patient in the ER for
11 increasing angina, and for some reason I'm not able to
12 come down and see the patient, I tell the ER physicians
13 to start the patient on IV nitroglycerine. And by
14 necessity, the patient needs to be admitted.

15 So that's just one element of the
16 arbitrariness. I would have chosen a less subjective
17 endpoint, which would be coronary artery bypass
18 grafting or angioplasty. At least you have to document
19 -- even that is highly subjective, depending on what
20 the practice patterns are, but at least you have to
21 document the burden of disease or the ischemia.

22 DR. WING: I'd be most happy to share with

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

184

1 you this paper because, as I say, this group -- I was
2 not on the endpoint working group. It was a group of
3 cardiologists, trialists who all very carefully met and
4 thought about these different outcomes, and felt that
5 the hospitalized angina was the most in keeping with
6 both our original goal, clinical practice, other
7 trials, and was best ascertained.

8 DR. KAUL: If I can ask a follow-up question,
9 you demonstrated that there was an impact in the
10 intensive lifestyle intervention group on glycemic
11 control, systolic blood pressure, and HDL cholesterol.

12 DR. WING: Yes.

13 DR. KAUL: Is the extended endpoint
14 responsive to these pathophysiologic changes? That
15 would be an additional justification. What is the
16 evidence that hospitalization for angina responds to
17 modification of glycemic control, systolic blood
18 pressure, and HDL cholesterol?

19 DR. WING: I hear your concerns. And as I
20 say, it was very carefully vetted and discussed. This
21 was the decision. I'd be happy to share the paper.

22 DR. THOMAS: Before I go to the next

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

185

1 question, I just wanted to make one quick comment.

2 Because of copyright issues, actually, Dr. Wing won't
3 be able to share the paper with the panel.

4 DR. WING: Oh.

5 DR. THOMAS: But everyone does have the
6 reference and an internet connection, so you're more
7 than welcome to look on your own at the paper, in your
8 spare time.

9 Dr. Bergman?

10 DR. BERGMAN: So as a physiologist, I can't
11 help wondering what the pathophysiology is of weight
12 regain. And I was wondering, you have this wonderful
13 group where they lost the most the first year, and then
14 they didn't gain back. So I wondered, did you look for
15 a genetic signal or any other pathophysiological signal
16 that might explain that? Because we could learn a lot
17 from that.

18 DR. WING: We have several ancillary studies
19 funded, looking at genetic factors in Look AHEAD and in
20 DPP, where we're looking at do genes predict how people
21 will lose weight or whether they will regain weight?
22 And those analyses are ongoing right at the moment.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

186

1 DR. THOMAS: At this point, we will break for
2 lunch. For those who had questions that we didn't get
3 to, we're keeping a list, and we will have time later
4 today to get to these questions, as well as any
5 additional questions.

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

11 Panel members, please remember that there
12 should be no discussion of the meeting during lunch,
13 amongst yourselves, or with any members of the
14 audience. Thank you.

15 (Whereupon, a lunch recess was taken.)

16 DR. THOMAS: We will now proceed with our
17 afternoon presentations, starting with Dr. Bray. I
18 would like to remind public observers at this meeting
19 that while this meeting is open for public observation,
20 public attendees may not participate except at the
21 specific request of the panel.

22 Dr. Bray?

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

187

1 DR. BRAY: Thank you very much, Mr. Chairman
2 and members of the panel. It's a pleasure to be here.
3 I was listening to the introductions this morning and
4 recollecting that my interest in obesity began at
5 Harvard and Tufts some 45 years ago and has gone
6 through UCLA, and the University of Southern
7 California, and a few other places. So I'm familiar
8 with many of your institutions, and I hope I can add to
9 the information you have for considering the issue of
10 developing drugs for the treatment of obesity.

11 These are my disclosures, a few in number.
12 The Takeda Global Development was actually over more
13 than a year ago. The other two are still going on
14 intermittently. This is what I propose to do in the
15 next 30 minutes. Talk about obesity as a risk for life
16 and health, and the fact that weight loss, as you've
17 already heard several times, reduces essentially all of
18 these risks, that we need drugs for weight loss because
19 they enhance the effects of lifestyle. And any place
20 they've been used together, there's been an added
21 benefit, with one exception when very low-calorie diets
22 are used.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

188

1 All drugs have risks, and those associated
2 with anti-obesity drugs are of many kinds.
3 Cardiovascular has been only one of them and to have a
4 single kind of trial to handle all risks may be an
5 interesting challenge. And I think there are things we
6 can do to mitigate some of these risks and I'll suggest
7 some of those at the end.

8 So first, obesity increases the risk of
9 mortality. And morbidity -- and I've picked this slide
10 from the collaborative studies, prospective studies
11 collaboration of Whitlock's paper, because it includes
12 a number of studies, 57, in which individuals were
13 pooled. It's a mortality study showing mortality for
14 men and women. And as you can see, there's an increase
15 in mortality in both genders as BMI increases. And the
16 study went on to look at that excess mortality by five
17 BMI units for several different causes, because it was
18 large enough to do that.

19 Overall mortality was 30 percent per five BMI
20 units. But there were several diseases for which it
21 was considerably higher, specifically diabetes being
22 the most important, but also hepatic disease, renal

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

189

1 disease, and vascular disease was at a lower level. So
2 diabetes is clearly the major increased risk for
3 mortality. Hepatic disease is just behind.

4 There are a number of morbidities associated
5 with obesity, and this slide lists many of these. I
6 will only list a few in the discussion. And I've
7 divided them into two broad groups, those that have, if
8 you like, a metabolic basis, the sorts of things that
9 Dr. Eckel talked about this morning for cardiovascular
10 disease, liver, gall bladder, diabetes, and cancer.
11 But there's a second group which are mass related, that
12 is, the stigma. You can tell someone's got problems
13 because they're fat, sleep apnea, and osteoarthritis,
14 to name three. And I'll talk about benefits for those
15 specifically, because we don't want to let our concern
16 about cardiovascular events overshadow the importance
17 of some of these other factors that benefit from weight
18 loss.

19 BMI has its biggest effect on diabetes. This
20 is an older slide from Walter Willett and colleagues,
21 showing, in red, the increasing relative risk for
22 diabetes for men and women, compared to hypertension,

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

190

1 cholelithiasis, and coronary heart disease, which are
2 comparable in their rates and considerably lower than
3 the relationship for diabetes in terms of increase
4 related to
5 BMI.

6 Weight loss benefits essentially all of these
7 -- and I want to show this in several categories. This
8 is the overall reduction in mortality in the surgical
9 series from the Swedish Obese Subjects study. It wasn't
10 a randomized study, but it was a matched control group
11 where a control was matched on something like 15
12 variables at the same time that a patient was operated
13 on, and then followed. And there was a significant
14 reduction in overall mortality.

15 Earlier this year, they published two figures
16 -- this is one of the two -- showing that this
17 reduction was in cardiovascular disease. Fatal MI and
18 total myocardial infarctions were both significantly
19 reduced in the surgically-treated participants. Not
20 shown on the slides here, but in their paper, stroke
21 was also decreased.

22 So it had a major impact on vascular system,

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

191

1 but in addition, it reduced the incidence of new cases
2 of cancer. So it has an impact outside of
3 cardiovascular disease. But you get this at a
4 mortality risk. Something like four individuals in the
5 surgical series died, or .2 percent. So it's a
6 significant death rate associated with this clear,
7 long-term benefit on life expectancy, cardiovascular
8 disease, and cancer incidence.

9 The benefits of weight loss are, in almost
10 all cases, linearly related to the change in weight.
11 This is again from the Swedish Obese Subjects study.
12 At two years, where they had stable weight changes,
13 they pooled the data from both the operated and control
14 groups and looked at the changes in these various
15 variables, cholesterol and high-density cholesterol
16 being two interesting ones that are not quite accepted,
17 but certainly cholesterol itself is. But all the
18 others -- triglyceride, insulin, uric acid, glucose,
19 systolic and diastolic blood pressure -- were linearly
20 related to the change in weight.

21 Cholesterol, interestingly enough, is not.
22 You need to lose something like 20 to 30 kilograms of

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

192

1 weight in order to begin to see a reduction in
2 cholesterol. So cholesterol and LDL cholesterol are
3 poorly related to weight change. HDL cholesterol and
4 all of these others clearly are and in a nearly
5 linearly fashion.

6 But there are other important benefits of
7 weight loss, and I wanted to show you two of these,
8 both of them from the Look AHEAD trial, which Dr. Rena
9 Wing talked about this morning. And the first is an
10 improvement in mobility of older people. As you've
11 said, I've been in this field 45 years, so I've gotten
12 a little older in that time, and I begin to understand
13 what mobility is like.

14 This is from a paper that was published in
15 the New England Journal of Medicine today, and they
16 gave us permission to use these figures from it. These
17 are the stagings that were used to evaluate mobility
18 and group people into one of four stages. Stage 1 is
19 the most mobile. Stage 4 is the least mobile. And you
20 can see the various components that went into making
21 that mobility assessment.

22 When you look at this impact on the diabetes

1 support and education group over the four years that
2 they were followed, you can see a decline, particularly
3 in the stage 4 group, the most immobile. And mobility
4 in terms of healthcare costs is a big player in terms
5 of hospitalization and nursing home care. So anything
6 you can do to reduce the decline in mobility will have
7 substantial health and economic benefits.

8 If you look at the intensive lifestyle group,
9 there's a substantial reduction, particularly in the
10 more severe grades of mobility decrease, stages 3 and
11 4. So this is one important benefit of weight loss,
12 particularly in the group that's served by the Look
13 AHEAD trial, older diabetics, that has a major health
14 and economic impact for all of us.

15 The second of these has been mentioned, but
16 I'll show an important component of this in the next
17 slides, and that's sleep apnea. This is the Sleep
18 AHEAD study that Foster published from the Look AHEAD
19 subgroup that looked at this. You can see that 13
20 percent had no sleep apnea, but that means 87 percent
21 had one or another grade of sleep apnea.

22 In the four-year weight loss data shown here

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

194

1 on the left, the intensive lifestyle group lost weight
2 compared to the DSE group, as Dr. Wing showed you
3 earlier. But what's particularly interesting is that
4 the AHI, the Apnea Hypopnea Index, a way of assessing
5 the degree of sleep apnea, declined in the intensive
6 lifestyle group and actually remained lower for all
7 four years of follow-up, in contrast to the
8 deterioration in this index for the others.

9 So sleep apnea and mobility are two important
10 additional elements of the obese state, which are
11 improved by weight loss that have important health
12 implications for all of us.

13 So why do we need drugs to treat obesity?
14 You've already heard two wonderful trials that showed 7
15 and 8 percent weight loss. And I would argue that we
16 need them because they enhance the weight loss we can
17 get with lifestyle alone. And this is the trial that
18 Sjostrom performed with many other groups in a
19 multicenter trial with orlistat, published in 1998.

20 You can see, at the end of the first year,
21 the difference between the lifestyle/placebo and the
22 orlistat group. It's about 5 percent weight loss. And

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

195

1 if you note, the weight loss with orlistat, it's about
2 10 percent in this group, and I will come back to that
3 in a moment.

4 The second feature of this slide is that at
5 the one-year point, a pre-randomization switch occurred
6 so that some subjects were switched to placebo who had
7 been on active drug, some from active drug to placebo.
8 And you can see that those that had been on drug and
9 were switched to placebo gained weight. Those that
10 were on placebo switched to active drug lost weight, to
11 reach essentially the same levels as those who had been
12 on the same drug for two years. So it adds to the
13 effectiveness of the lifestyle operation.

14 You should have saw this figure earlier from
15 the Diabetes Prevention Program. It's the modeled
16 change in weight and incidence of type of diabetes per
17 100-person years of follow-up. And I've used it as a
18 base for selecting what I would label as adequate; that
19 is a 50 percent reduction in risk of developing
20 diabetes. And what I would prefer is something like a
21 10 kilogram loss, 10 percent loss, which will reduce
22 the risk by about 90 percent. We didn't quite achieve

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

196

1 that on average, but these would be the criteria that I
2 would want for drugs.

3 So I'm going to assess a variety of drugs,
4 and I'm going to do it by using actual weight loss, not
5 placebo-subtracted or mean-weighted differences. And
6 I'll show you why I'm going to do that and hope you
7 will keep this in mind when you consider how you decide
8 what the weight loss to be achieved by a drug in a
9 trial for weight loss should be.

10 These are the weighted mean differences on
11 the left. The -3.01 is the difference between the
12 control and lifestyle in the 21 studies that LeBlance
13 put into a meta-analysis late last year. The 2.98 --
14 and I'd submit that's not different from 3.01 -- is the
15 placebo- subtracted difference between lifestyle and
16 orlistat plus lifestyle, so you could conclude, if I
17 don't show you anything else, that they are in fact the
18 same.

19 This is what those two bars look like in the
20 21 trials that they had. The lifestyle groups on
21 average lost 4 percent, and the placebo ones, about 1.
22 So there's a clear weighted mean difference of 3

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

197

1 kilograms, but if you look at the lifestyle versus
2 orlistat, the weighted mean difference is still 3
3 percent, but the actual weight loss is greater.

4 If you recall that slide I showed you earlier
5 of the modeled weight loss, you're going to get more
6 bang for your buck, if I may use that expression, with
7 the 8 percent loss than you're going to get with the 5,
8 or the 4, or the 1 percent. It's curvilinear related
9 and it can be deceptive to use placebo-subtracted data
10 to express information about weight loss studies
11 because what the patient sees, what the physician sees,
12 and what's important in the risk reduction is the
13 actual weight loss, not the placebo-subtracted weight
14 loss.

15 So with that little diatribe of mine about
16 why I don't like placebo-subtracted weight losses, I'll
17 show you a set of data in which almost all of it is
18 actual weight loss, not placebo-subtracted.

19 These are a number of drugs, beginning with
20 phentermine, which you've heard a lot about, the number
21 of studies and the length of these studies, and the
22 weight losses. And one could add some more to this. I

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

198

1 only picked a few trials, listed at the bottom.

2 But you can see, for most of these, the
3 figures are between 3 and, in one case, 9 kilograms,
4 but that's way too high for pramlintide. But most of
5 them are in the range of 5 or 6.

6 The second group of studies actually stack up
7 better, and what you'll note about them is that in the
8 lower half, they're all combinations, and they're all
9 combinations of one or two. And in several of these
10 combinations, phentermine shows up again.

11 So one of the strategies for drug development
12 for use of drugs for treatment of obesity -- and I'll
13 come back to this again later -- in my view is
14 combination therapy. And the challenge in a sense is,
15 if you set a low bar for approval of drugs -- set a
16 high bar so that you don't get drugs approved, you can
17 never use them in combination. If you only get drugs
18 that have 10 percent weight loss, you're not going to
19 have many because, in monotherapy, there are very few
20 drugs that have, by any mechanism so far, demonstrated
21 their ability to do that. But if you don't have them,
22 you can't combine them to get the kind of weight loss

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

199

1 you begin to see when you do combine them.

2 So I think it's a real challenge in designing
3 a way to get effective, safe, but not necessarily
4 magnificent drugs available so that they can be
5 combined, because the only drug available at the moment
6 for long- term use approved by the Food and Drug
7 Administration is orlistat.

8 I wanted to introduce this study again,
9 published this week, and I'm trying to show you it.
10 Even though I've been at it 45 years, I'm still more or
11 less up to date. This was a paper comparing, in a
12 randomized control trial, non-blinded surgery using two
13 different surgical techniques with medical therapy.
14 And it was designed to look at diabetics whose body
15 mass indexes were in the range for which drug therapy
16 for obesity is now approved, between 27 and 43.

17 You'll note on the lower right panel the
18 weight loss of these three groups. The surgical
19 groups, both sleeve gastrectomy and gastric bypass,
20 lost about 10 BMI units, something like 25 percent of
21 their initial body weight. Medical therapy lost only 5
22 percent, which is about what you get with most medical

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

200

1 therapies. But since all of these patients were
2 diabetics like those in Look AHEAD, the goal was to
3 reduce the hemoglobin A1c to below 6.

4 You can see, for the medical therapy group,
5 to get the reductions they got in hemoglobin A1c, they
6 had to use substantially more medication. The two
7 surgical groups had more weight loss, reduced the
8 percent who had diabetes by 37 or 42 percent, and
9 substantially reduced the amount of anti-diabetic
10 medications.

11 So if we don't have better drugs coming on
12 the market that will allow the medically-treated group
13 to come closer to approximating the surgical group, my
14 guess is that the surgical group will replace -- or
15 will be our treatment for obese patients, with the
16 attendant mortality that it has. There were no deaths
17 in these 150 patients, but there clearly is a finite
18 mortality with that procedure.

19 So what predicts weight loss? The answer is
20 initial weight loss. Dr. Wing showed you that before,
21 but there are data from both orlistat and sibutramine
22 trials showing that early weight loss, less than one

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

201

1 year, between three months or less, will predict
2 subsequent weight loss. And I want to show you that
3 here with sibutramine.

4 This is the mean weight loss at three months
5 of more or less than 4 kilograms. If you'd lost 4
6 kilograms at one year, your weight loss on average was
7 about 15 percent of initial body weight. So the people
8 who respond early respond well. And those who don't
9 respond early don't respond well at all. And I think
10 this is an important consideration in developing drugs
11 and in their clinical use.

12 But all drugs have adverse events and some of
13 these can be serious. I've published this table a
14 number of times on the calamities that have occurred to
15 the medications that have come along and, in some cases
16 diets, over the years, leading to a whole variety of
17 bad outcomes.

18 On this slide, I've tried to summarize the
19 adverse event on the left with examples on the right
20 that have produced it. And you'll see that some of
21 these are pulmonary. Some are cardiovascular, the
22 middle three. And then some are not either of those.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

202

1 They're suicidal or emotional difficulties. And there
2 have been examples of drugs or diets in all of these
3 categories.

4 I've compared on this slide several of the
5 drugs that are available, orlistat, fluoxetine,
6 bupropion, and topiramate. This is taken from a meta-
7 analysis that was the basis for the guidelines by the
8 American College of Physicians to show you the pattern
9 of side effects that are seen.

10 The top ones, diarrhea or constipation, one
11 or other, headache, nausea, fatigue, and dry mouth are
12 characteristic of many of the anti-obesity drugs. The
13 ones at the bottom tend to be specific for different
14 drugs, and as you can see in yellow where the numbers
15 were high, they scatter across the drug groupings.

16 In the widely-used drugs, orlistat,
17 sibutramine, and rimonabant -- rimonabant was never
18 approved in this country, but was in Europe -- you can
19 see that the blood pressure pulse response stands out
20 in the sibutramine group, not in the others. What
21 stands out in the orlistat group, I left out as
22 gastrointestinal side effects, which tend to be related

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

203

1 to the kind of food you eat in relation to the drug
2 when you take them.

3 I wanted to spend one minute on the SCOUT
4 trial, which I gather we will hear more about from the
5 agency shortly. It was a sibutramine cardiovascular
6 outcome trial which was designed at the request of the
7 European Medicines Agency because of the concern about
8 its being used and producing cardiovascular bad
9 outcomes.

10 In order to get enough people into a trial
11 and have endpoints in the life of the investigators,
12 they picked people at high risk, none of whom, or
13 almost none of whom, by package insert, should have
14 been included in the trial.

15 There was a run-in period of six weeks where
16 all participants took sibutramine to exclude those who
17 had bad responses. Then they were randomized to
18 lifestyle or placebo and continued for up to six years.
19 The average was 3.4 years of continuous treatment,
20 whether they responded to treatment or not.

21 You can see on the next slide, this one, the
22 weight loss curves, the initial blue one, is the weight

1 loss on sibutramine, and they all lost weight nicely.
2 Initially, sibutramine is a pretty good weight loss
3 drug. At the dashed line, they were randomized.

4 One of the interesting features of this is
5 that the sibutramine placebo group did not regain
6 weight. It's very likely older participants in DPP and
7 Look AHEAD. And this was an older group who were at
8 risk. Once you've lost weight in that group, you in
9 fact may not regain it very rapidly or at all if
10 treatment is discontinued, and this is a good example
11 of that, out over six years. Those who were treated
12 with sibutramine in blue clearly lost more weight.

13 I don't have Kaplan-Meier plots here, but
14 these are the correct endpoints. I just had straight
15 lines in between. The mortality was 10 percent. There
16 was a 10 percent incidence of primary outcome event,
17 shown here as the non-fatal MI, non-fatal stroke,
18 resuscitation after cardiac arrest, or cardiovascular
19 death. There was an 11.4 percent incidence in the
20 sibutramine-treated group.

21 But of that group, only 30 percent of the
22 patients actually lost more than 5 percent with

1 sibutramine, meaning 70 percent were in a category
2 where you probably should not have continued to treat
3 them beyond that initial four months, but they were
4 continued for up to three years.

5 If you split that group in the previous
6 slide, the 11.4 percent, into those who lost weight on
7 sibutramine and those who did not, you see that the
8 sibutramine-treated patients who lost weight, which is
9 what you give a weight loss drug for, actually had an
10 incidence rate that is below that of the 11.4 percent,
11 10 percent in this group. They're below the lifestyle
12 group here. So if people lose weight, they can get
13 benefits even if they have underlying cardiovascular
14 disease.

15 So how can we mitigate some of the risks?
16 Develop drugs with a high safety profile. And I won't
17 say more about that because that's what we'd all like
18 to have happen. But there are a number of other things
19 one can do. There are data with both phentermine and
20 sibutramine showing that the long term, that is, one-
21 year weight loss, is similar whether the drug is used
22 continuously or intermittently. And since the risk

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

206

1 with any drug is associated with its being there --
2 well, even allergies -- one could recommend that drugs
3 be used intermittently rather than continuously.

4 Use of combinations of drugs. And I've
5 already alluded to. This is a pair of drugs,
6 phentermine and pramlintide, which produced a weight
7 loss that hadn't quite plateaued, but is somewhere
8 below 10 percent. And it's clear to me that
9 combinations are essential if we are to move our weight
10 loss goals closer to what the surgeons can achieve.
11 But to do that, you have to have agents that you can
12 combine. Only one of these is approved for obesity.
13 That's phentermine, and that only for short-term use.

14 Establish that weight loss actually
15 continues. And I'm going to show you a slide that was
16 shown earlier by the FDA this morning. It was the
17 trial that led to the recommendation that weight loss
18 trials be one year of randomized placebo-controlled
19 evaluation because Prozac or fluoxetine, which was used
20 in this study, had nice weight loss, not very great,
21 but consistent out to 20 weeks or so. But when the
22 trials were extended, you can see weight was regained

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

207

1 even though the drug was continued.

2 I don't understand why that occurs, but
3 clearly, there's an important lesson. They're both for
4 drug evaluation and for understanding the
5 pharmacological basis of weight control. So you need
6 to establish that a drug works and continues to work.

7 Select drugs that cause weight loss when
8 treating overweight patients for conditions other than
9 obesity. Diabetes is clearly one of these. We have a
10 number of drugs that produce weight gain and some which
11 produce weight loss. Bill Knowler referred earlier to
12 the metformin data with the Diabetes Prevention
13 Program. This is, in fact, the data that will appear or
14 has appeared this month in Diabetes Care and was
15 approved for its use.

16 I guess, Bill, is that okay to say, you and
17 me approved it?

18 DR. KNOWLER: It's already published.

19 DR. BRAY: It's already published. Okay.

20 Good.

21 What's interesting about it is that we've
22 partitioned the metformin users into their level of

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

208

1 adherence to the medication. And you'll note that the
2 bottom line are those who were considered to be highly
3 adherent. The next line up are those who were somewhat
4 adherent. The white line is those that were less
5 adherent. And the yellow line were people who were
6 hardly ever or never adherent. They took a little at
7 the beginning, probably, but not much thereafter.

8 You can see a clear adherence relationship,
9 and the group that had high adherence out over 10 years
10 had a weight loss that was in the range of 4 percent
11 from baseline. So it is a weight loss drug, although
12 not approved for that purpose.

13 Finally, as I've said several times, and will
14 say again, only treat patients who respond to the
15 drugs. In the sibutramine SCOUT trial, it was clear
16 that if you're going to conduct a trial like that, in
17 my judgment, you don't continue people on a drug which
18 has potential for toxicity when they don't respond to
19 the drug. That clearly seems to me to have been bad
20 medical judgment on somebody's part.

21 So this is again from the Look AHEAD data.
22 This partitions the lifestyle group up into various

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

209

1 percentiles of success. You'll note that the 90th
2 percentile did extremely well, weight loss that
3 averages nearly 18 percent. The 75th percentile was
4 about 12 percent. The 50 percentile was our 8.6
5 kilogram percent weight loss.

6 The two other groups, however, the bottom
7 25th percentile, probably should have had something
8 other than Look AHEAD if they were going to lose weight
9 because, for them, the lifestyle program that we used
10 was not successful. And this will be the case for all
11 approaches that I know of. And we should not be
12 treating people with whatever program it is if they
13 don't respond to it.

14 So I have a couple of conclusions and then
15 one set of suggestions. Excess weight gain and central
16 adiposity increase, many health risks. Weight loss
17 improves the risk profile in almost all instances.
18 Obesity can be seen in the mirror, but high cholesterol
19 and blood pressure cannot. Because of this, obesity is
20 a stigmatized condition, and patients may
21 inappropriately want to use weight loss medications
22 because they know they are fat.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

210

1 Medications augment the effect of lifestyle
2 for weight loss, which is why they need them. And as I
3 said earlier, combinations can be more beneficial than
4 individual drugs alone. But all drugs have risks, and
5 not all patients respond equally to any given
6 medication, or I could have said "therapy." Most
7 benefits from medication for obesity are achieved by
8 six months, and you can predict the success by periods
9 as early as three months.

10 Lifestyle placebo effects vary between
11 trials, and weight loss from baseline might therefore
12 be a better criterion than weight loss below placebo to
13 evaluate response.

14 Therefore, my suggestions would be that
15 physicians prescribing anti-obesity drugs should
16 ascertain that patients are responding adequately, and
17 if not, modify treatment, that they shouldn't be
18 continued if weight loss doesn't occur. But several
19 strategies can be used to mitigate potential risks,
20 including intermittent treatment, combination therapy,
21 selecting effective drugs, and stopping treatment for
22 unresponsive patients.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

211

1 So there's the facility to which I return
2 when I work, the Pennington Biomedical Research Center.
3 And I thank you for your attention. I'm happy to
4 answer any questions if there are any.

5 DR. THOMAS: Thank you, Dr. Bray.

6 Actually, we're going to go to -- Dr. Soukup
7 is going to do the next presentation. At the end of
8 both presentations, we'll have time for questions from
9 the panel.

10 DR. SOUKUP: Thank you and good afternoon.
11 My name is Matt Soukup, and I'm a team lead within the
12 division of Biometric 7, within the Office of
13 Biostatistics at CDER. Today, I will present the
14 challenges associated with the design and statistical
15 analysis of dedicated cardiovascular safety trials as
16 they apply to products intended for the treatment of
17 weight loss.

18 The initial focus of my presentation will
19 introduce some of the fundamental concepts associated
20 with outcome-driven trials, as well as statistical
21 measures used in comparing two treatments.

22 Dedicated cardiovascular safety trials are

1 designed as event-driven trials, which are a special
2 case of information-based clinical trial designs. A
3 feature of the information-based clinical trial design
4 is that the statistical information is fixed in advance
5 rather than using the number of subjects to determine
6 the size of the trial.

7 For an event-driven trial, the statistical
8 information corresponds to the number of events which
9 I'll define here as the letter D. Therefore, the trial
10 will continue to enroll or follow patients until the D
11 events are observed. In order to observe the D events
12 which the trial is designed around, N subjects are
13 followed for a prespecified time. This is defined by
14 the letter T.

15 Multiplying the number of subjects, N, by the
16 duration of observation for each subject, T, we end up
17 with N-times-T patient years. While the number of
18 patient years can be anticipated, the actual value will
19 depend upon the observed event rate because D events
20 must be observed in order to preserve the power for
21 which the trial was designed.

22 For event-driven cardiovascular safety

1 trials, it's imperative to pre-define the primary
2 safety endpoint. Commonly, the associated
3 cardiovascular risk is assessed using a composite
4 endpoint, though there remains some debate about which
5 components of the composite to include.

6 The traditional major adverse cardiovascular
7 events composite endpoint, commonly referred to as
8 MACE, consists of the three components, cardiovascular
9 death, myocardial infarction, and non-fatal stroke.
10 Alternate MACE composite endpoints have been utilized.
11 These consist of the traditional MACE components, plus
12 additional components such as hospitalization for
13 unstable angina and revascularizations. I'll refer to
14 the more inclusive composite as MACE Plus.

15 While this presentation is not meant to go
16 into detail about which components to include in the
17 composite, it is worth noting that the definition of
18 the primary composite endpoints may have downstream
19 implications on statistical analysis and interpretation
20 of the trial.

21 As MACE Plus includes more components in the
22 traditional MACE composite, we know that the event rate

1 based upon MACE Plus will be higher than the event rate
2 based upon the traditional MACE. Therefore, fewer
3 patient years would be needed to observe the pre-
4 defined D event for a fixed amount of risk to be ruled
5 out.

6 If MACE Plus is used, then certain components
7 of this composite have the potential to add noise in
8 observed event rates. This has a potential to impact
9 the trial results. If the trial objective is to show
10 that the associated cardiovascular risk is not greater
11 than some pre-defined threshold, the noise has the
12 potential to favor the active in meeting the trial
13 objective. However, if the trial objective is to show
14 that the associated cardiovascular risk is
15 statistically better in actively-treated subjects, this
16 noise can result in not meeting the trial objective.

17 As a side note, in safety trials which are
18 designed based upon a composite endpoint, individual
19 components of the composite should be assessed in
20 addition to the composite as a whole. This is in part
21 to ensure that results are consistent for all the
22 components, as well as to assure that the results are

1 not driven by a single component.

2 To compare the results of actively-treated
3 subjects to those subjects treated with the control,
4 the comparison is based upon some statistical measure.
5 There are various choices in how to measure the
6 association. And here I present three that are common
7 and used in comparing event rates.

8 The risk difference is absolute difference in
9 the probability of an event between the two treatments.
10 Here I denote this is RD, and this is equivalent to the
11 risk of that active minus the risk of the control. The
12 relative risk is the relative difference in the
13 probability of an event between the two treatments.
14 Here, I denote this is RR and this is equal to the
15 ratio of the risk of the active to the risk of the
16 control.

17 The hazard ratio is a ratio of the hazards of
18 the two treatment. Ultimately, this is the ratio of
19 the rate at which subjects in the two treatments
20 experience an event where a slower rate suggests a
21 longer time of being event-free. This is a common
22 measure when using survival analysis techniques. Here,

1 I denote this is H_zR .

2 An important issue to consider in assessing
3 the association of cardiovascular safety between two
4 treatments is to determine what statistical measure
5 provides the relevant clinical information about the
6 risk.

7 Is it more meaningful to understand the
8 absolute difference in risks, i.e. the risk difference,
9 or the relative difference in risks, i.e. the relative
10 risks? If the event rate of the control arm is known,
11 or the trial design enrollment criteria targets a
12 population with an anticipated event rate, and if the
13 trial goes to rule out either relative or absolute
14 risk, one can calculate the alternate measure of
15 association.

16 A key point is that the risk difference takes
17 into account the background event rate. To illustrate
18 this, suppose we are interested in ruling out a
19 relative risk, which is defined as 1.3, 1.8, and 2, as
20 shown in the table here. For each relative risk, we
21 can calculate the associated risk difference that takes
22 into account the event rate of the control arm. Here,

1 you can see that the risk difference is calculated as
2 the relative risk minus 1, times the event rate.

3 As an example, if the event rate of the
4 control is 1 percent, then we know that ruling out a
5 relative risk of 1.3 corresponds to ruling out an
6 absolute risk of .3 percent or 3 excess events per
7 1,000 treated subjects.

8 However, if the event rate of the control is
9 1.5 percent, then ruling out a relative risk of 1.3
10 corresponds to ruling out an absolute risk of .45
11 percent or 4.5 excess events per 1,000 treated
12 subjects. This point I will illustrate more broadly in
13 the next slide.

14 The figure on this slide depicts a number of
15 excess events plotted against the relative risk of the
16 active to control. Separate lines are provided for
17 various choices of the background event rate, namely 1
18 percent, 1.5 percent, and 2 percent.

19 For example, if we are interested in ruling
20 out 10 excess events, and if the background rate was 2
21 percent, this would be equal to ruling out a relative
22 risk of 1.5. However, if the background event rate was

1 1 percent, then to rule out 10 excess events, this
2 would be equivalent to ruling out a relative risk of 2.

3 In the previous slides, we've shown that when
4 event rate is known and the trial is designed to rule
5 out a relative risk or absolute risk, one can obtain a
6 value for the alternate measure of association.

7 In the illustrations provided, the following
8 conclusions can be reached. If annual event rate turns
9 out to be higher than the planned event rate, which is
10 considered in the design stage of the trial, then the
11 selected relative risk margin will not preserve the
12 amount of excess risk to exclude.

13 For example, suppose the trial is planned to
14 have an event rate of 1 percent and the amount of
15 excess risk to be ruled out is set at 3 excess events
16 per 1,000. Note again here, I am working with the
17 relative risk of 1.3. If the actual event rate turns
18 out to be 1.5, then this would correspond to ruling out
19 4.5 excess events per 1,000 patients, which is higher
20 than the 3 excess events per 1,000, as initially
21 planned.

22 In contrast, if the annual event rate turns

1 out to be lower than the planned event rate, then the
2 selected risk margin will rule out a smaller amount of
3 excess risk to be excluded.

4 For example, suppose the trial is planned to
5 have an event rate of 1.5 percent and the amount of
6 excess risk to be ruled out is set at 4.5 excess events
7 per 1,000 patients. If the actual event rate is 1
8 percent, then this would correspond to ruling out 3
9 excess events per 1,000 patients, which is lower than
10 the 4.5 excess events per 1,000, as planned.

11 While the previous slides alluded to the
12 goals of a dedicated cardiovascular safety outcome
13 trial, I will now present these more formally in the
14 following few slides. In subsequent slides, I
15 presented information on the basis of relative risks.
16 This is done for simplicity and to avoid confusion when
17 also including information on risk difference.
18 However, it should be noted that the same concepts
19 apply when using a risk difference as the measure of
20 association.

21 In the design of a dedicated cardiovascular
22 outcomes safety trial, there are two potential trial

1 objectives. One potential objective is to show risk
2 improvement. Under such an objective, the goal is to
3 show that the cardiovascular risk associated with the
4 active is statistically better than the cardiovascular
5 risk associated with the control.

6 This is similar in construct to an efficacy
7 superiority trial. The associated null hypothesis is
8 that the relative risk is greater than or equal to 1,
9 where relative risk of one corresponds to equal event
10 rates between the active and the control. The
11 corresponding alternative hypothesis is that the
12 relative risk is less than 1.

13 The other trial objective is to show that the
14 cardiovascular risk of the active is statistically no
15 worse than that of the control. This I refer to as a
16 non-excessive risk comparison, which is similar in
17 construct to a non-inferiority comparison when
18 assessing efficacy, and I'll expound more on this point
19 later.

20 The key for a non-excessive risk comparison
21 is that some threshold value needs to be defined. This
22 I refer to as the risk margin and denote as δ^* .

1 The null hypothesis for a non-excessive risk comparison
2 is that the relative risk is greater than or equal to
3 the risk margin. The corresponding alternative
4 hypothesis for this comparison is that the relative
5 risk is less than the risk margin.

6 In this slide, I provide an illustration of a
7 trial objective to show risk improvement. To assess
8 risk improvement, the upper bound of the 95 percent
9 confidence interval is compared to 1. If the upper
10 bound of the 95 percent confidence interval is below 1,
11 risk improvement can be claimed. An example
12 illustrated on scenario 1 would meet the risk
13 improvement trial objective.

14 The following illustration depicts a trial
15 objective as showing non-excessive risk. This is
16 similar to showing risk improvement, except that we now
17 add in a dashed line that corresponds to the risk
18 margin, or delta star, which represents the amount of
19 risk to rule out. If the upper bound of the 95 percent
20 confidence interval is below the risk margin, the trial
21 meets the non- excessive risk objective.

22 Here, we see that scenarios 1, 3, and 4 meet

1 the non-excessive risk objective. Also note that the
2 point estimate, as shown by the black circle, does not
3 have to be below 1 in order for the upper bound of the
4 95 percent confidence interval to be below the risk
5 margin.

6 From the illustration just shown, we can see
7 that a trial objective of risk improvement is a special
8 case of a trial objective to show non-excessive risk.
9 The special case arises when the risk margin is set to
10 equal unity. It's also worth noting that the paradigm
11 of assessing non-excessive risk is similar in construct
12 as assessing non-inferiority in efficacy trials.
13 However, there are some key differences.

14 First, in non-inferiority efficacy trials,
15 the control arm is an active product, whereas in non-
16 excessive risk safety trials, the choice of control can
17 be a placebo, background therapy, standard of care, or
18 even an active control with a known safety profile.

19 Second is in how a margin is selected. A
20 non- inferiority margin for efficacy trials is based
21 upon historical information of the active control,
22 whereas the risk margin for safety trials typically

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

223

1 relies on the feasibility of the study size, clinical
2 judgment, or some other information.

3 I will now focus on sample size calculations
4 in how trial size is influenced by several factors.
5 Recall that a dedicated cardiovascular safety outcomes
6 trial is an information-based clinical trial design and
7 that information is represented by observing a certain
8 number of events, which I'll define as D here.

9 To calculate the number of events needed, one
10 can use the formulas shown here. Here, we see that
11 several factors are needed to calculate the number of
12 events: the desired power of the trial, the type 1
13 error rate, the true relative risk, and the risk
14 margin. I will go into detail on how each of these
15 factors are selected and the implications they have in
16 the calculation of the number of events.

17 The power of the trial is the probability of
18 rejecting the null hypothesis when, in fact, it is
19 false. From the formula presented, we can see that as
20 power increases, the number of events needed would also
21 increase. In general, for trials to assess safety,
22 there may only be one randomized trial to infer effect

1 sizes, and, as such, one should consider the highest
2 power that is feasible.

3 The type 1 error rate, i.e. alpha, is the
4 probability of rejecting the null hypothesis when in
5 fact it is true. As in efficacy trials, type 1 error
6 rates should be controlled at the two-sided alpha
7 equals 0.05 level. From our formula, we can see that
8 decreasing the type 1 error rate would require more
9 events. This implies that trials that incorporate
10 multiple comparisons would need to account for the
11 reduction in alpha when powering the trial. Such a
12 scenario can be envisioned when a trial incorporates
13 interim analyses into meeting the trial objective.

14 Recall that the risk margin for safety trials
15 is typically not based upon historical data on an
16 active control, as in non-inferiority efficacy trials.
17 Rather, study feasibility, clinical judgment, and other
18 considerations play a role in determining the risk
19 margin for non-excessive risk objectives in safety
20 trials. In general, lower risk margins require more
21 events. This implies that showing risk improvement
22 will require a larger sample size in showing non-

1 excessive risk when all other factors in the formula
2 are held constant.

3 As mentioned earlier in my presentation,
4 there still remains the question of whether a risk
5 margin should be defined using a risk difference, i.e.
6 the absolute risk, or a relative risk.

7 To understand the relative cardiovascular
8 safety from active treatment to control, interest can
9 lie in the relative risk. The actual relative risk is
10 a population parameter that is unknown. In statistics,
11 we use a sample such as a clinical trial to draw
12 inferences about the population parameter.

13 In order to determine how large such a sample
14 or clinical trial would need to be, we must make an
15 assumption on what is believed to be the true value of
16 the population parameter. In our case, we were
17 interested in assuming a value for the true relative
18 risk as denoted by row.

19 The process for selecting a value of the
20 population parameter to be used in sample size
21 calculations differs in trial designs for efficacy than
22 those designed for cardiovascular safety. A typical

1 paradigm to power trials for efficacy consists of
2 conducting a small trial or trials to obtain a reliable
3 estimate of the population parameter.

4 Such an approach -- or such an estimate is
5 used to power later confirmatory trials. However, for
6 cardiovascular safety, such a paradigm is oftentimes
7 not feasible, as few cardiovascular events would be
8 expected in early, small trials, especially in trials
9 which are short in duration as well as conducted in low
10 cardiovascular risk populations.

11 Therefore, in order to power a dedicated
12 cardiovascular safety outcomes trial, a blind guess as
13 to the value of the true relative risk must be used in
14 trial size calculations. In general, though, the
15 closer the true relative risk is to the risk margin,
16 more events are needed. This is due in part to the
17 fact that more events would result in a narrower
18 confidence interval, and the confidence interval would
19 need to be narrower for risk margins which are close to
20 the true relative risk.

21 To provide an example of how many events are
22 needed, we can consider the following scenario. First,

1 we use a relative risk margin of 1.5, which corresponds
2 to ruling out a 50 percent increase in cardiovascular
3 risk. Next, we assume that the true relative risk is
4 equal to unity, implying that risk is equivalent in
5 both the active and the control. And lastly, we set
6 the power at 90 percent and use a two-sided type 1
7 error rate of 0.05. Plugging these into the formula
8 previously shown results in 256 events.

9 I will now go into some detail about how the
10 choice of the risk margin and the assumed true relative
11 risk impact this number-of-events calculation.

12 In the following figure, I use the
13 information from the previous slide. Namely, power is
14 fixed at 90 percent, type 1 error rate at 0.05, and the
15 risk margin is set at 1.5, and allow the true relative
16 risk to vary. And this is plotted along the X axis.
17 The resulting number of events needed for the various
18 choice of the true relative risk are plotted along the
19 Y axis. Here, we can see that as the true relative risk
20 increases, the number of events increases.

21 This is a table of results to show specific
22 values of the true relative risk and the number of

1 events. For example, if there is a 15 percent relative
2 reduction in cardiovascular risk, then 131 events would
3 be needed to rule out a relative risk margin of 1.5.

4 Alternatively, if there is a 15 percent relative
5 increase in cardiovascular risk, 596 events would be
6 needed to rule out a relative risk margin of 1.5.

7 In this figure, I assess the relationship of
8 the risk margin and the number of events when power is
9 fixed at 90 percent, type 1 error rate at 0.5, and I
10 assume that the true relative risk is 1. Here, we can
11 see that as the risk margin increases, fewer events are
12 needed.

13 This is a table of results to show specific
14 values to the risk margin and the number of events.
15 For example, if the goal is to rule out a relative risk
16 of 1.3, 611 events are needed when we assume the true
17 relative risk is 1. However, if the relative risk
18 margin is set at 2, then 88 events would be needed when
19 the true relative risk is assumed to be 1.

20 This figure depicts the number of events
21 needed for a risk improvement trial objective, i.e.,
22 this is equivalent to a relative risk margin of 1, with

1 various choices of the true relative risk, which are
2 all below 1 and shown here on the X axis. As seen with
3 the non- excessive risk objective, this shows that as
4 the true relative risk converges to 1, more events are
5 needed.

6 Again, this table provides the number of
7 events needed for various choices of the true relative
8 risk when the objective is to show risk improvement.
9 For example, if there is a relative risk reduction of
10 30 percent, then 331 events would be needed to
11 demonstrate risk improvement. However, if there is a
12 relative risk reduction of 10 percent, then 3,786
13 events would be needed to demonstrate risk improvement.

14 The previous slides depicted power
15 calculations showing impacts on trial size in terms of
16 the number of events. I will now transition it into
17 looking at a trial size in terms of the number of
18 anticipated years that would be needed to observe the D
19 events.

20 Recall that the patient years are calculated
21 as the number of patients times the number of years the
22 patient is followed. For example, 1,000 patients

1 followed for two years would result in 2,000 patient
2 years of follow-up.

3 To translate the number of events, D , into
4 patient years, the trial is designed with a targeted
5 event rate, which I denote as θ . Then, to
6 calculate the number of anticipated patient years
7 needed to observe the D events, we divide the number of
8 planned events by the targeted event rate. Here, this
9 is expressed as D divided by θ .

10 In the calculations that follow, I will show
11 similar scenarios, as shown previously, but now express
12 the trial size in terms of patient years for target
13 event rates of .5 percent, 1 percent, 1.5 percent, and
14 2 percent. As with the earlier calculations, I'll fix
15 power to be 90 percent and the two-sided type 1 error
16 rate to be 0.05.

17 In the figures shown here, I depict the
18 relationship of the true relative risk and the
19 estimated number of patient years needed to observe the
20 planned events for each of the four assumed event rates
21 when trying to rule out a risk margin of 1.5. Here, as
22 expected, we can see that as the true relative risk

1 increases, the number of patient years increases, and
2 this is most dramatic when an event rate is 0.5
3 percent.

4 Here is a table of results to show specific
5 values of the number of patient years for the fourth
6 annual event rates if we assume the true relative risk
7 is 1. For example, if the annual event rate is 0.5
8 percent, or 5 in 1,000, and the true relative risk is
9 1, then 51,200 patient years would be anticipated to
10 rule out a relative risk margin of 1.5. However, if
11 the event rate is 2 percent, then 12,800 patient years
12 would be anticipated for the same objective.

13 We now examine the relationship of the
14 relative risk margin and the estimated number of
15 patient years needed to observe the planned events for
16 each of the four assumed event rates, when the true
17 relative risk is 1. As expected, we can see that as the
18 relative risk margin gets closer to 1, the number of
19 patient years increases quite substantially.

20 Here is a table of results that shows
21 specific values of the number of patient years for
22 various annual event rates if we assume the true

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

232

1 relative risk margin is set at 1.4. For example, if
2 the annual event rate is 5 in 1,000 and the goal is to
3 rule out a relative risk margin of 1.4, then 74,200
4 patient years would be anticipated. However, if the
5 event rate is 2 percent, then 18,550 patient years
6 would be anticipated for this same objective.

7 The figure here depicts a number of patient
8 years anticipated to show risk improvement with varying
9 the assumed true value of the relative risk. As seen
10 with the non-excessive risk objective, this shows that
11 as the true relative risk converges to 1, more patient
12 years would be anticipated.

13 This table provides the patient years that
14 would be anticipated for the four annual event rates
15 when there is a 15 percent reduction in the relative
16 risk. For example, if the event rate is 5 in 1,000,
17 then 318,400 patient years would be needed to show risk
18 improvement if the true relative risk is 0.85.
19 However, if the annual event rate is 20 in 1,000, then
20 79,600 patient years would be anticipated to show risk
21 improvement.

22 The following points summarize what was shown

1 in this portion of the presentation in regards to
2 assessing trial size for dedicated cardiovascular
3 safety outcome trials. First, we see that the trial
4 objective, either risk improvement or non-excessive
5 risk, has large implications on the trial size. In
6 general, unless there's an anticipated large reduction
7 in cardiovascular risk, i.e., the true relative risk is
8 much less than 1, then one can anticipate trials with
9 the goal of showing risk improvement to be larger than
10 trials who show non- excessive risk. Overall, holding
11 all other factors constant, as the risk margin
12 increases from 1, then trial size calculations would
13 decrease.

14 Second, the true relative risk, which is a
15 driving factor in trial size calculation, is unknown,
16 with limited data available to derive reliable
17 estimates to its value prior to conducting the trial.

18 As was shown, the assumed value for this
19 parameter has large implications on the size of the
20 trial. You will see in a subsequent presentation today
21 that the values in the trial size calculation may turn
22 out to be overly optimistic, and one needs to be

1 cognizant to this fact when designing and powering
2 cardiovascular safety outcome trials.

3 Lastly, events are observed by following
4 patients for a fixed period of time and this provides
5 the number of patients years. Trials that would be
6 enriched to observe patients at higher cardiovascular
7 risk would require fewer patient years than trials in
8 lower cardiovascular risk populations.

9 I will now switch gears and look at
10 statistical issues that go beyond trial size
11 calculations. These issues we anticipate need to be
12 addressed in the way trial results would be analyzed,
13 as well as interpreted.

14 To date, in the fiscal analysis of the
15 composite cardiovascular endpoint, either MACE or MACE
16 Plus, we use time-to-event methodology. Modeling is
17 performed using a Cox proportional hazard model with
18 treatment as the factor. We have also accepted models
19 that incorporate more than treatment, as long as these
20 factors are prespecified in the analysis plan.

21 When looking at non-excessive risk, we
22 compare the upper bound of an appropriately alpha-

1 adjusted confidence interval for the hazard ratio to
2 the risk margin. Alpha adjustments would need to be
3 considered for multiple looks at the data. If no
4 multiplicity adjustment is needed, a 95 percent
5 confidence interval is appropriate.

6 The question does remain on what analysis
7 population should be considered as primary. This I
8 present in the next several slides.

9 First, it is important to understand
10 disposition rates as they have been observed in one-
11 year efficacy trials, as these tend to be high. While
12 results may vary from trial to trial, in recent
13 applications, the percent of subjects that complete a
14 full year ranges from 55 percent to 75 percent. Within
15 a given trial, that dropout rate is higher among
16 subjects randomized to placebo than subjects randomized
17 to active.

18 In a dedicated cardiovascular safety outcome
19 trial, it is expected that even a smaller percent of
20 subjects would complete the trial while on treatment.
21 This can be an artifact of several reasons.

22 First, recent proposals for dedicated

1 cardiovascular outcome trials include rules for
2 discontinuation. These rules consist of things such as
3 lack of efficacy after so many months of treatment or
4 sustained increases in vitals. Additionally, the trial
5 duration to observe cardiovascular safety would
6 typically be longer in duration than one year in order
7 to observe cardiovascular safety and then also to have
8 enough events as the study was initially powered.

9 While subjects can be discontinued from
10 treatment, it's worth noting, in a dedicated
11 cardiovascular safety trial, subjects that are taken
12 off treatment would be encouraged to remain in the
13 trial. Therefore, we can define two periods of time for
14 which a subject would be studied, an on-treatment period
15 and an off-treatment period. It's worth keeping in mind
16 such disposition rates, as this will impact how events
17 are counted and the amount of exposure used in the
18 statistical analysis, which is presented in the next
19 slides.

20 In this slide, I now illustrate one of two
21 potential analysis populations, the total time analysis
22 population for some hypothetical scenarios. In the

1 illustration, the solid black lines denote time the
2 subject was exposed to treatment. The blue, dashed
3 lines denote the time the subject was off treatment,
4 but still in study. And the red circles indicate when
5 an event occurs.

6 In a total time analysis population, the time
7 contributed to the analysis is consisted of the on-
8 treatment epic plus the off-treatment epic. This
9 illustration depicts the on-treatment analysis
10 population for the scenarios shown on the previous
11 slide. Here, information contributed to the analysis
12 will be based solely on the on-treatment epic.

13 Based upon the illustrations, an analysis
14 based upon the total time analysis population would
15 incorporate censoring at the time the subject is no
16 longer followed, whether on treatment or off treatment.
17 In such a population, all events are counted,
18 regardless of when they occur, on or off treatment;
19 whereas analysis of the on-treatment analysis
20 population would incorporate censoring at the time the
21 subject discontinues treatment. Events that occur while
22 off treatment would be counted.

1 Note that this analysis population may or may
2 not include some window of time that would be
3 prespecified in advance. Both analysis populations
4 will preserve the randomization included in the study.
5 It's just a matter of how to account events that occur
6 off study and how to define the exposure time
7 contributed in the analysis.

8 Also, the choice of the analysis population
9 may address different clinical questions. Therefore,
10 it's important to consider which analysis population
11 would have more clinical meaning in dedicated
12 cardiovascular safety trials for products indicated for
13 the treatment of obesity.

14 The next topic I will discuss is one where a
15 two-stage approach is used to evaluate cardiovascular
16 safety. Under this two-stage approach, the goal is to
17 show non-excessive risk, where excessive risk is
18 assessed using a risk margin that is a sliding bar.
19 The two risk margins must be selected for such an
20 approach.

21 Delta star 1 corresponds to the risk margin
22 utilized in stage 1 and delta star 2 corresponds to the

1 risk margin selected for stage 1, where the risk margin
2 for stage 2 is less than the risk margin used for stage
3 1. Under such an approach, the trial is powered to
4 meet the risk margin for stage 2, and the risk margin
5 for stage 1 is assessed using a fraction of the total
6 number of events needed to meet risk margin 2.

7 This two-stage approach can be utilized where
8 the pre-approval of the product is based upon the risk
9 margin 1, with a post-marketing requirement that, post-
10 approval, the trial be based upon risk margin 2. In a
11 presentation later today, you will see how this two-
12 stage approach is used in assessing the cardiovascular
13 risk for type 2 diabetes, where the pre-approval risk
14 margin is 1.8, with a post-marketing requirement that
15 the risk margin of 1.3 be ruled out.

16 The last concept I will share is based upon a
17 need to assess conditional power if a two-stage
18 approach is implemented. Conditional power is
19 important to consider because there remains the
20 possibility that a treatment is approved based on the
21 pre-approval risk margin when, in fact, the true
22 relative risk is greater than the post-approval risk

1 margin.

2 To clarify this point, let's consider an
3 example, where the pre-approval risk margin is defined
4 as 2.2 and the post-approval risk margin is set at 1.5.
5 The trial is powered to rule out a relative risk margin
6 of 1.5, assuming that the true relative risk was 1, for
7 which no real data existed, and this was, in essence, a
8 blind guess.

9 While truly unknown in nature, a simulation
10 study was conducted in which we set the true relative
11 risk to be 1.5. Ultimately, this means that the blind
12 guess was poor, as 1.51 is quite a bit larger than 1.
13 However, when applying this simulated data example
14 where the true relative risk is 1.51, there's a 34
15 percent probability that the upper bound of the 95
16 percent confidence interval is below 2.2, which would
17 meet the pre-approval risk margin. This would occur,
18 despite the fact that the trial would not be able to
19 rule out 1.5 post-marketing, since the true relative
20 risk of 1.51 is greater than the post-marketing risk
21 margin of 1.5.

22 This example illustrates the need to evaluate

1 the pre-approval results in terms of the likelihood the
2 trial can meet the post-approval risk margin when a
3 two- stage approach is implemented. In addition, this
4 also highlights the need to look at more than just the
5 upper bound of the 95 percent confidence interval and
6 its relation to the risk margin when making decisions
7 using a fraction of the total planned number of events
8 for which the trial was designed.

9 I will now finish with some closing remarks.
10 Overall, there exists some unique challenges in the
11 design and analysis of dedicated cardiovascular safety
12 outcome trials. Clinical considerations are necessary
13 in how such trials are ultimately powered, as well as
14 analyzed.

15 The following points summarize the key issues
16 that will impact the statistical analysis in powering
17 of these cardiovascular safety outcome trials. One,
18 the objective of the trial, whether it be risk
19 improvement or non-excessive risk, will play a major
20 role in the size of the trial. In general, unless
21 there's anticipated large reductions in cardiovascular
22 risk, i.e. the true relative risk is much less than 1,

1 then one can anticipate trials with the goal of showing
2 risk improvement to be much larger than trials who show
3 non-excessive risk. Overall, holding all other factors
4 constant, as the risk margin increases from 1, then
5 trial size calculations would decrease.

6 Two, in a setting of a non-excessive risk
7 objective, it remains a question of whether the risk
8 margin should be defined in terms of absolute risk,
9 i.e., risk difference, or relative risk. For absolute
10 risk margins, one should consider such a margin in the
11 context of the targeted annual event rate. It's worth
12 noting that targeting an annual event rate that is
13 higher than the observed event rate will preserve the
14 absolute risk margin. However, if the targeted event
15 rate is lower than the observed event rate, then the
16 absolute risk margin is not preserved.

17 Three, for the statistical analysis, it
18 remains a question about which analysis population,
19 total time or on treatment, should be considered as
20 primary. Both populations preserve the randomization,
21 but the number of events and time contributed to the
22 analysis are treated differently, as well as these may

1 answer different clinical questions.

2 Lastly, I'd like to acknowledge several
3 statistical and clinical colleagues, and their input,
4 and feedback into this presentation. And then thank
5 you. And I believe, before we turn it over to Dr.
6 Colman, we have Q and A.

7 DR. THOMAS: Thank you for your presentation.
8 We'll now take questions for both Dr. Bray and Dr.
9 Soukup.

10 Dr. Hiatt?

11 DR. HIATT: Thank you for that. That was, I
12 think, an incredibly important presentation that will
13 underlie our thinking, particularly tomorrow.

14 So a couple of thoughts. One comment is, in
15 terms of thinking about cardiovascular risk trials in
16 the context of understanding an obesity drug, clarify
17 one thing for me, number one, are we hypothesis testing
18 or just making observations based on the cumulative
19 evidence? So the more events you have, the tighter the
20 margin. Is that your approach?

21 Secondly, if we're looking at the absolute
22 versus the relative risk difference in trials where the

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

244

1 event rates are, by definition, extremely low and hard
2 to enhance, would you favor then the relative risk
3 margin approach? It sounds like you would.

4 DR. SOUKUP: The second question, I don't
5 know if I have a preference. I think, statistically,
6 we can account for it. I think part of it is,
7 clinically, if there's one that is maybe more
8 meaningful. Again, the key is, as I mentioned, that if
9 you consider an absolute risk, you have to consider
10 what the event rate is going to be on your control or
11 background rate.

12 Your first question in terms of, is it a
13 formal hypothesis test, yes. This would be formally
14 tested, and that's how it is powered, as a formal test.

15 DR. HIATT: Then the last clarification is,
16 you allow the point estimate to go above 1 on some of
17 your scenarios, correct?

18 DR. SOUKUP: Yes.

19 DR. HIATT: So I guess this is probably not a
20 question for you, but I just wonder myself if that's
21 really advisable because, if you get enough numbers, as
22 you showed, you can have point estimates of maybe 1.1

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

245

1 or even maybe 1.15, getting close to sibutramine, but
2 cap the upper bound below some threshold we think is
3 clinically meaningful like 1.5.

4 So numerically, you could get there. You
5 could have a drug that might absolutely increase risk
6 on the point estimate, but rule out a certain excess
7 risk on the upper bound.

8 DR. SOUKUP: Correct.

9 DR. THOMAS: Dr. Brittain?

10 DR. BRITTAIN: Thank you. I have a couple
11 questions. First of all, with the true relative risk
12 being so huge in terms of determining the number of
13 events or sample size, however we want to think about
14 it, and you didn't feel that there would be much basis
15 for being able to know what that would be, would there
16 be any room for doing something, either interim
17 analysis or adaptive, so that if there really were a
18 benefit, that you could take advantage of that and not
19 have to study as many patients?

20 DR. SOUKUP: Yes. Statistically, I think we
21 almost encourage it because it is such a blind guess.
22 We really don't know anything about that, so I think

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

246

1 it's smart to actually incorporate that type of
2 analysis into your planned analysis in the end.

3 DR. BRITTAIN: The second question I had --
4 and maybe I didn't understand it exactly, the approach
5 you have. You didn't call it a per protocol. It's a
6 little different, where you censor patients who go off
7 drug.

8 If this censorship is informative, is that
9 really going to preserve the randomization? Are you
10 really going to have a valid comparison?

11 DR. SOUKUP: I think that is a key issue, and
12 I don't think we know up front. Again, those are the
13 things, I don't know if we can anticipate it happening.
14 I think we would look at it when the data would come
15 in, but I don't know if we could plan up front how to
16 do that, or we could do sensitivity analyses to address
17 that. But I think that is a real concern.

18 DR. THOMAS: Dr. Proschan?

19 DR. PROSCHAN: Yes. I have questions for
20 both speakers, but I'll start with Dr. Bray. You did
21 some analyses where you showed -- I think this was
22 slide 37, where you showed people who lost at least 5

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

247

1 percent versus less than 5 percent of their body weight
2 on drug and how they did. And then you also had one
3 for adherence.

4 I'm really worried about that kind of
5 analysis, and I'm wondering -- because Paul Canner did
6 something similar, showing that people who adhered to
7 drug did really well. And then he showed that if they
8 adhered to the placebo, they also did very well. And
9 I'm wondering if you did similar analyses in the
10 placebo group to see what the difference between those
11 two groups was.

12 The other thing is I totally don't understand
13 your slide 22, where I thought you were arguing that
14 the placebo-subtracted difference somehow was zero, and
15 yet there was a big difference when you looked at the
16 bars separately. And I don't understand how that's
17 possible.

18 DR. BRAY: This one? I'll animate it, if
19 that helps. This is from LeBlance's meta-analysis.
20 And I took their numbers for each of these bars and
21 plotted them to show the weighted mean differences,
22 which are identical, but the fact that the actual

1 weight loss is substantially greater in the right-hand
2 bar, orlistat plus its lifestyle, compared to its
3 lifestyle alone. And if you use the modeled weight,
4 you would anticipate greater impact on all of the risk
5 factors with the yellow bar than the green one, the red
6 one than the blue one. But you wouldn't see that from
7 the weighted mean differences.

8 Weighted mean differences, unless you look at
9 the two components, don't tell you what the actual
10 weight loss is. And unless there's something
11 mysterious about what we're trying to do, it's weight
12 loss that we're trying to achieve. And weighted mean
13 weight loss doesn't tell you what that is.

14 DR. PROSCHAN: My understanding was that
15 you're saying you want to look just in a treatment
16 group and see, okay, there's an 8 kilogram or whatever
17 weight loss and how important is that. But without
18 knowing what the change was in the control group, I
19 don't see how you can interpret that.

20 DR. BRAY: I interpret it -- if I can go back
21 to my -- from this slide, that if the DPP modeling is
22 correct and you have an at-risk population, you will

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

249

1 get more reduction in your conversion from impaired
2 glucose tolerance to diabetes if you get greater weight
3 loss.

4 DR. PROSCHAN: Right. No, I understand that.

5 DR. BRAY: If you looked at -- go back up to
6 this one, it's not the weighted mean difference that's
7 going to give you that extra weight. It's actually
8 looking at the weight. And what I'm saying is that
9 when you only present weighted mean difference weights,
10 you miss that maximum actual weight loss. You can't
11 tell from those weighted mean differences whether the
12 orlistat treatment is better than the lifestyle
13 treatment. At least, I can't.

14 DR. PROSCHAN: Yes. My point is that you
15 would expect a certain reduction just from regression
16 to the mean, so how much of that weight loss is real, I
17 can't tell without knowing what the placebo change was
18 and other factors, regression of the mean being one of
19 them.

20 DR. BRAY: Now, this is a meta-analysis of
21 lots of studies.

22 DR. PROSCHAN: Right.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

250

1 DR. BRAY: Does regression to a mean become
2 an issue in meta-analyses?

3 DR. PROSCHAN: Sure. Because in each of
4 those trials, presumably, people started out with high
5 weight exceeding a certain threshold. So in every one
6 of those trials, if you weighed them again even without
7 any intervention, the weight will go down. It will
8 tend to go down. And there could be other factors,
9 too. I mean, it might not just be -- it might be that
10 they're at their highest weight ever and would have
11 gone down anyway.

12 So I still think that you can't really
13 interpret that without subtracting out the placebo
14 difference.

15 DR. BRAY: You and I disagree, and I won't
16 accept a paper that I review that doesn't contain both
17 numbers. I don't care if you use a placebo-subtracted
18 number, but since the placebo can be highly variable --
19 and I didn't put those slides in here. But placebos
20 are highly variable. And when you have highly variable
21 placebos, you get a very big change in the placebo-
22 subtracted number, which from a clinical and weight

1 loss perspective, is irrelevant.

2 I object to people using only placebo-
3 subtracted data in publications. And as I say, when I
4 review them, they can't do that. They've got to give
5 me both sets of numbers because, as I tried to argue,
6 it's the actual weight loss you get that's important,
7 not what the placebo does, but what the placebo plus
8 the drug do. The combination of those two gives you
9 your maximal weight loss. It's what the patient gets.
10 It's what the doctor is going to see. And it's what --
11 if that figure from DPP is reasonable -- your impact
12 will be on risk factors. That's my argument.

13 DR. THOMAS: Dr. Proschan, did you have one
14 more question for Dr. Soukup?

15 DR. PROSCHAN: Yes, I did, actually.

16 Yes. One of the questions, you have a
17 formula for the sample size, which has that 4 in front
18 of it. And I agree with that formula when you have
19 equal size groups, but the situation is even worse
20 because the recommendation is to have 3,000 on
21 treatment and 1,500 on the control. So when you have
22 unequal sample sizes, that factor out in front is

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

252

1 actually more like 4 and a half. And so it's even worse
2 than the picture he painted, which was already bleak in
3 terms of the number of outcomes.

4 Yes. I also had a problem with the statement
5 about preserving randomization. I wouldn't agree with
6 that as -- I wouldn't characterize it as preserving
7 randomization, that formula. Right.

8 What slide number is that?

9 DR. SOUKUP: Sixteen.

10 DR. PROSCHAN: Sixteen. Yes. And just the
11 other point. I do think you have to be careful when
12 you present the individual components of these
13 outcomes, like if you have MACE and then you present
14 the individual components.

15 To me, it does not make any sense to do an
16 analysis on non-fatal MI, for example, if you don't
17 also include the fatal ones. Fatal MI is informative
18 censoring. You see this all the time in journals, and
19 it makes no sense to look at only non-fatal events and
20 then censor fatal events. So I disagree with that
21 practice.

22 DR. THOMAS: Do you have any comments, Dr.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

253

1 Soukup?

2 DR. SOUKUP: I don't have anything
3 additional.

4 DR. THOMAS: Dr. Alexander?

5 DR. ALEXANDER: Yes. I also have a question
6 for each speaker. And so since Dr. Soukup is up there,
7 I'll ask. I've always struggled with, what are the
8 right events to consider here. And so you laid out
9 MACE and made this MACE Plus. But we heard earlier
10 today also about weight loss being associated with
11 reductions in arrhythmias or heart failure.

12 So I'm interested in, what's the impact of
13 adding additional events that are differentially
14 affected by the treatment? For example, if you were to
15 add in atrial fibrillation and new heart failure, but
16 your drug or your intervention only increased MI,
17 death, and stroke, what would adding those additional
18 cardiac events in do to your ability to detect
19 differences?

20 DR. SOUKUP: So as I show it here on slide 5,
21 I presented it as these additional components are
22 noisy. And by noisy, I mean it's random chance that

1 you're going to get these things. There's no bias here
2 where it favors one treatment over another. And if
3 you're looking at a non-excessive risk, that noise is
4 all going to be centered around 1, so you're getting
5 events, so it is going to be a good thing to help you
6 get to rule out a risk margin.

7 However, if you're trying to show there is an
8 improvement in the cardiovascular risk, that noise is
9 centering you around 1, when really, you want to get
10 away from 1. So that's where the issue comes in with
11 noise.

12 The bias you mentioned is correct. If it is
13 favoring one treatment or the other, we would have to
14 consider some of that, but I haven't really laid that
15 out.

16 DR. ALEXANDER: So if one were to be trying
17 to exclude harm and you added in all cardiac events or
18 maybe all adverse events, you'd have a very large
19 number of events and no ability to detect a difference
20 in any particular important one, unless you know what
21 that important one is beforehand.

22 DR. SOUKUP: Right.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

255

1 DR. ALEXANDER: Right. Thanks.

2 Then I have a question for Dr. Bray, and this
3 is really something I've been thinking about from the
4 two earlier presentations by Dr. Wing and Dr. Knowler.
5 And it's mostly a question about how the analysis was
6 done.

7 We've been talking about weight loss causing
8 a reduction in diabetes, or hypertension, or
9 hyperlipidemia. But what I've seen is mostly
10 interventions like intensive lifestyle intervention, or
11 metformin, or bariatric surgery causing a reduction in
12 both weight and diabetes.

13 So I'm curious. The analyses that we've seen
14 and the modeling that's been done out of DPP and Look
15 AHEAD, were they assessing both events at the same
16 time, or is it weight loss now, results and reductions,
17 and diabetes later?

18 Do you understand that question?

19 DR. BRAY: Yes. I'm going to ask my
20 colleagues if they want to assist with that
21 interpretation.

22 Bill?

1 You measure them as you go along in the
2 trial. And in one of them that Bill responded to, the
3 Hamman paper, where we looked at whether it was weight,
4 or lower fat, or exercise that impacted the changes, we
5 did analyze each of those components. And as Dr.
6 Knowler was saying, the noise around -- the lipid
7 measurements -- sorry -- around the measurement of
8 dietary fat intake change and around the measurement of
9 exercise differences is much, much larger than the
10 error around the measurement of weight. So you
11 probably can't separate those out. The errors in
12 measuring blood pressure and lipids in blood are much
13 smaller.

14 But, Bill, you're standing by the microphone.

15 DR. KNOWLER: If I understood your question
16 about is the change in weight causing the change in
17 diabetes risk, I don't think we can ever answer that
18 with certainty. We've done an experimental study.
19 We've produced weight loss. It's reduced the risk of
20 diabetes. But was it the weight loss or was it some
21 other aspect of the intervention? We've done the best
22 we could. We've tried to see, well, was it asking

1 people to walk 150 minutes? Was it asking them to
2 reduce their fat calories?

3 Well, number one, those two things are hard
4 to measure, if people really did that or not, whereas
5 weight we can measure very precisely. So that's going
6 to favor weight. But was there some other measure of
7 well-being, people feeling good because they're in an
8 intervention program, and that worked through some
9 means other than weight? That's theoretically
10 possible, but there was such a strong association with
11 weight, you would have to argue that that other thing
12 was also related to weight.

13 DR. ALEXANDER: I mean, I guess I was just
14 struck by it. I think you could just flip those over
15 and say preventing diabetes causes weight loss. Right?
16 Because they're measured at the same time. The
17 association is the same in either direction.

18 DR. KNOWLER: No, not really because in those
19 analyses, once someone developed diabetes, they were
20 censored. We didn't look at what happened after that.
21 So we're always looking at a change in weight, and then
22 subsequently, did they develop diabetes in the next

1 observation period? So I don't think the causal
2 interpretation is reversed.

3 DR. BRAY: And you have a lot of other trials
4 where diabetes was not the endpoint, but all of them,
5 regardless of intervention, produced the same changes
6 in blood pressure and the like. So I think it's a
7 fairly consistent finding, but it's like asking are we
8 sure the sun is going to rise tomorrow; and the answer
9 is we won't know until tomorrow gets here. It's that
10 kind of question, which you sometimes can't get an
11 answer.

12 DR. THOMAS: Thank you. Dr. Temple?

13 DR. TEMPLE: This is sort of a follow-up of
14 what Dr. Proschan asked. As he says, we would almost
15 never accept subgroups that were formed after the trial
16 was carried out, as a way to look for increased benefit
17 with greater response. I wonder if anybody has any
18 thoughts about the possibility of having a screening
19 period, in which you look for compliance or success and
20 then randomized after that. Then it's a properly
21 randomized trial.

22 So I guess my question is, can you guess

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

259

1 reasonably well about whether a drug, or whatever the
2 intervention is, will work in a few weeks so that you
3 could then randomize according to how well they did?

4 This may be tomorrow's discussion.

5 DR. KNOWLER: If you recall the Weintraub
6 trial from 1994 or thereabouts, where he looked at
7 fenfluramine and phentermine combination, and his
8 initial six weeks was a single blind run-in period and
9 the randomization was done after that. And his placebo
10 group essentially was flat, and his drug treatment
11 group continued to lose weight.

12 I mean, that's as close -- now, the orlistat
13 people did something like that. They had a single
14 blind run-in period of a couple of weeks. And again,
15 you're always going to get a weight loss. And, of
16 course, the issue is what you do with the change in
17 lipids and the like during that single blind run-in
18 period. The rimonabant people did that and got
19 all kinds of flak from many sides because they didn't
20 have all of the appropriate measures to know where they
21 were at before they randomized. But several of them
22 had done the randomization after an initial single

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

260

1 blind run-in period and then looked at changes. But it
2 is fraught with some problems because you get a lot of
3 your impact on some of these risk factors during that
4 initial weight loss period.

5 DR. KONSTAM: Bob, can I just comment?

6 DR. THOMAS: I think we probably should
7 discuss this more tomorrow.

8 DR. KONSTAM: Can I just ask, how would you
9 write the labeling for that?

10 DR. THOMAS: Actually, I think we should
11 probably -- that's more, I think, a discussion for the
12 questions tomorrow. And since some of the speakers
13 won't be here tomorrow, we can probably try and get to
14 those questions. And if we have time, we can always
15 come back to that later. And Dr. Colman may hit upon
16 that a little bit in the SCOUT design when he's
17 presenting that.

18 So if we can, go to Dr. Kaul.

19 DR. KAUL: Yes. I had a comment and a
20 question. I agree with Dr. Proschan about the composite
21 endpoint analysis. I think it's a good idea to do what
22 Jim Neaton calls a consumer report analysis, where you

1 list not only the non-fatal components, but also the
2 total, so that you get an idea of what the case
3 fatality rate is. And that's helpful in weighing the
4 relative importance of the components.

5 The question I have for you is, are you
6 suggesting that we fix the boundaries of unacceptable
7 risk? I mean, my whole read of this is, this is
8 essentially a benefit-risk construct. And we as
9 clinicians are willing to tolerate a greater degree of
10 risk, depending on what the benefit tradeoff is.

11 So if you have a drug that is associated with
12 a 5 percent weight loss, are you going to rule out the
13 same unacceptable risk compared to a drug that is
14 associated with, let's say, a 10 or 15 percent weight
15 loss? How do we reconcile this benefit-risk, both from
16 a regulatory perspective as well as from a clinician's
17 perspective?

18 DR. SOUKUP: I think that's ultimately what
19 the discussion is about, as I don't have a preference.
20 It's one where, for me, statistically, if you define
21 what it is, we can power the trials. We can get to
22 what we need to. We need input from clinical to help

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

262

1 us make those determinations right now.

2 DR. KAUL: So if you're using diabetes
3 guidance as a paradigm, my understanding of the
4 diabetes guidance is that those margins of unacceptable
5 risk are rather fixed, aren't they?

6 DR. SOUKUP: Yes. And you'll hear about that
7 later this afternoon.

8 DR. THOMAS: Dr. Jensen?

9 DR. JENSEN: This is a question that maybe
10 both speakers could collaborate in answering.

11 George, I took your point that for some
12 medications, continuing people on them who were not
13 responding, would end up exposing people to all the
14 risk with none of the benefit. And it's hard to make
15 an assessment about what it would be like in the real
16 world. But the flip side is, if you allow people to go
17 off, and then you censor them, then you don't know if
18 there was some event that happened later that was
19 because of the medication.

20 Are you aware of any data where there has
21 been follow-up of the people who have gone off some of
22 the compounds to see if there was a sort of latent

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

263

1 event? And this goes to some of the statistical
2 approaches of continuing follow-up after they go off
3 the compound, to look for later events rather than just
4 censoring them when they stop.

5 DR. BRAY: Not in the weight field. Mike, as
6 you know, it's difficult to get people back for weight
7 loss trials. I'm a PI on Look AHEAD and DPP, where our
8 return rate is 90 plus percent for years.

9 The best weight loss trial we've done was the
10 balance lost one, where we got 80 percent back at two
11 years, but that took arm twisting and almost sending
12 the police out to get people to come back in. It is
13 very, very difficult. Anybody who believes they could
14 do this better than that is living in a world of
15 fantasy. I mean, that's about as good a two-year
16 follow-up as has been reported.

17 In the ACT NOW trial with pioglitazone, where
18 we were looking for prevention of diabetes, the paper
19 that DeFronzo published, we did, when people developed
20 diabetes, censor them, but we continued to follow them
21 in the trial subsequent to that for other events.

22 It can be done sometimes, but in weight loss

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

264

1 trials, it's very difficult to get people to come back,
2 even when they should be and when you think they're
3 still on medication. And if you've got some
4 suggestions about how we do that, I'd love to hear them
5 because it's been very difficult.

6 So I don't have an answer to your question on
7 how you do that.

8 DR. THOMAS: Dr. Yanovski?

9 DR. YANOVSKI: Actually, this is a question
10 that's very related to what Mike Jensen just asked.
11 Correct me if I'm wrong, George, that you're proposing,
12 really, adaptive trial designs even for initial studies
13 done to seek FDA approval because, if your notion is
14 that we should either stop or crossover people who are
15 failing to succeed on drug A, then that's a real change
16 from what has typically been proposed.

17 Am I stating your position --

18 DR. BRAY: No. I was really talking about
19 the SCOUT trial, where the risk was there when you
20 didn't get weight loss. If you don't have any risk
21 signals with trials, as we do all the time, I'd keep
22 people on placebo or drug continuously.

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

265

1 There was a period -- and, Eric, I don't
2 remember if you were with the agency then, but when
3 most of the trials were crossovers. I mean, there were
4 three- month crossovers or six-week crossovers, but
5 short crossover periods. And it's very difficult to
6 have that second period like the first one.

7 Crossover designs in the obesity field were
8 pretty much abandoned in the 1970s as a strategy. And
9 I wouldn't go back to them. I think they're a bad
10 thing to do. And I've not been in favor, personally --
11 you haven't asked me -- of doing a run-in because of
12 all of the reductions in risk factor measurements that
13 occur in that run-in period, that you have a hard time
14 correcting for. So I prefer to do what the doctor
15 would do and start the drug and the placebo at the same
16 time. If there aren't any big risk signals, I wouldn't
17 continue on for the period of a year as a double-blind
18 randomized placebo-controlled trial.

19 I think you were talking about a
20 cardiovascular outcomes study, which is a different
21 kettle of fish, I think, than the standard clinical
22 trial, and I wasn't dealing with those.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

266

1 Does that answer your response?

2 DR. THOMAS: Dr. Gregg? Dr. Bergman?

3 DR. BERGMAN: I just want to respond a little
4 bit to what Bill Knowler said about finding the time
5 course of obesity versus diabetes, a function of time
6 and what causes what. I mean, we know from lots of
7 work that insulin resistance itself doesn't cause
8 diabetes and we know that obesity itself is not
9 directly related to insulin resistance, but they're
10 correlated with each other. And its beta cell
11 function, which either does or doesn't respond to the
12 insulin resistance, which causes diabetes.

13 So in any trial, I think having surrogate
14 measures of these things to follow the time course not
15 only of obesity, but some surrogate of insulin
16 resistance and a surrogate of beta cell function, which
17 is actually easier to get, to calculate the disposition
18 index or something is doable. And I guess if you want
19 some information about what the mechanism is by which
20 the weight loss causes an improvement in diabetes, I
21 think you can get it, and I think it's a good thing to
22 get, personally.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

267

1 DR. THOMAS: Dr. Hiatt?

2 DR. HIATT: A quick question for Dr. Bray on
3 slide 37 -- and you made this comment just a minute ago
4 -- that patients in the SCOUT trial who lost a lot of
5 weight had fewer events than those who didn't lose
6 weight.

7 So that's kind of a self-fulfilling prophecy
8 and I want to just send on a note --

9 DR. BRAY: Should be the next one, I think,
10 on this.

11 DR. HIATT: That one.

12 DR. BRAY: Yes.

13 DR. HIATT: Yes.

14 DR. BRAY: This would essentially partition
15 them at more or less than 5 percent.

16 DR. HIATT: Right. So as I recall, during
17 that meeting, the sponsor actually proposed that, gee,
18 if the patients weren't responding early in the trial,
19 we'd stop them, and maybe that would obviate all the
20 risk, because if you actually lost a lot of weight,
21 maybe that cardiac risk would go away. But the trial
22 was never designed to test that hypothesis.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

268

1 DR. BRAY: No, it wasn't.

2 DR. HIATT: So I want to be really careful
3 about how you'd interpret those kinds of data. I think
4 we've heard all today that if you lose a lot of weight,
5 you tend to do better than if you don't lose much
6 weight. It doesn't certainly say to me that that drug
7 doesn't carry risk.

8 DR. BRAY: No. And I wouldn't have treated
9 the people in the SCOUT trial who got the drug, either.
10 But I say, when you make a division by those who
11 actually got the benefit of the drug when they were in
12 the trial, then you saw something different than
13 ignoring, than taking all those people who didn't.

14 To go back a few slides before that, if I can
15 get back there, the one that looked at the effect of
16 predicting the weight in the first three months on
17 sibutramine, I wouldn't have gone beyond three months.
18 If you didn't get weight loss at three months, there's
19 little reason to continue the drug because you're
20 unlikely to get a response at one year. That's the
21 yellow line.

22 If you did get 4 kilograms or more at 3

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

269

1 months, you got quite a substantial weight loss. And
2 if you were not at cardiovascular risk, it seems to me
3 it was a good medication for those people.

4 DR. HIATT: So I think we'd all agree that
5 makes lots of common sense, but the trial designs
6 weren't really designed to ask it that way. I think
7 Dr. Temple just said that maybe we should do a
8 responder look at the run-in and not randomize people
9 who weren't responding. Right? Initially? Which I
10 think is what sibutramine did.

11 DR. TEMPLE: Yes. That would be pure. I
12 mean, we're going to talk about this tomorrow. But if
13 your pattern was to drop people who weren't doing very
14 well, that would be a sort of real-world kind of study,
15 was still randomized if you just dropped them after
16 they didn't respond.

17 DR. HIATT: Exactly.

18 DR. TEMPLE: And that might be okay. That's
19 one of the things on our list of questions.

20 DR. HIATT: Sure. I just wanted to point
21 out, since tomorrow hasn't occurred yet, that none of
22 the data we've seen so far has actually applied that

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

270

1 strategy prospectively.

2 DR. THOMAS: We'll now take a 15-minute
3 break. Panel members, please remember that there should
4 be no discussion of the meeting topic, during the
5 break, amongst yourselves or with any member of the
6 audience. We will resume at 2:55.

7 (Whereupon, a recess was taken.)

8 DR. THOMAS: We'll now start with our next
9 presentation. Dr. Colman?

10 DR. COLMAN: So I'm going to spend about 20
11 minutes. I want to point out some of the major design
12 features in the primary results from two cardiovascular
13 outcomes trials that were done with obesity drugs. And
14 these really are the only two trials that have been
15 attempted.

16 The first is the Comprehensive Rimonabant
17 Evaluation Study of Cardiovascular Endpoints and
18 Outcomes, better known as CRESCENDO. And this was done
19 with the obesity drug rimonabant. The second trial is
20 the Sibutramine Cardiovascular Outcomes or SCOUT study.
21 And that was done with the weight loss drug
22 sibutramine.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

271

1 Now, I'm going to quickly point out how the
2 folks who take part in the cardiovascular outcomes
3 trials differ from the folks who take part in the
4 standard phase 3 pre-approval trials for these obesity
5 drugs and then quickly summarize.

6 So rimonabant was a cannabinoid-1 receptor
7 antagonist or inverse agonist that was developed for
8 the treatment of obesity, beginning around the year
9 2000. At a 20-milligram once-daily dose, the placebo-
10 subtracted weight loss was about 5 percent over the
11 course of a year. Rimonabant-induced weight loss had a
12 favorable effect on HDLC and triglyceride levels. It
13 also had a beneficial effect on hemoglobin A1c and, for
14 the most part, blood pressure. The drug also had
15 adverse neuropsychiatric effects. Most notably, there
16 was a signal for an increased risk in suicidality.

17 So the drug was approved by the European
18 Medicines Agency in 2006, and in 2007, a FDA advisory
19 committee recommended against approval of rimonabant,
20 citing a belief that the risks of the drug outweighed
21 its benefits based on the data available at that time.

22 So CRESCENDO was started at the behest of one

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

272

1 or two countries in the European Union. And it was a
2 randomized, double-blind, placebo-controlled study of
3 over 18,000 individuals. Half received 20 milligrams a
4 day of rimonabant and the other half received placebo.
5 And the primary endpoint was major adverse
6 cardiovascular events or MACE. And this was a
7 composite of cardiovascular disease death, non-fatal
8 MI, and non-fatal stroke. So this is what we would
9 refer to as strict
10 MACE.

11 The trial began in December of '05, and for
12 reasons I will elaborate on in a moment was stopped
13 early in July of 2008. Here are some of the inclusion
14 criteria, age over 55 years, abdominal obesity as
15 measured by an increase in waist circumference. Had to
16 have a history of overt cardiovascular disease within
17 three years of starting the trial. And for those who
18 did not have a history of cardiovascular disease, they
19 at least had to have two major CV risk factors. And
20 these risk factors included type 2 diabetes, at least
21 two features of metabolic syndrome, in addition to an
22 increased waist circumference, renal artery disease,

1 asymptomatic cerebrovascular or peripheral artery
2 disease, advanced age, or an elevated hsCRP.

3 So there were two prespecified cardiovascular
4 risk subgroups to find at baseline. The first were
5 those individuals who entered the trial with a history
6 of overt cardiovascular disease. And then for those
7 who did not have a history of cardiovascular disease
8 but were at risk, they were the second subgroup. I'll
9 show you some data by these two different subgroups in
10 a moment.

11 CRESCENDO initially had 90 power to detect a
12 15 percent reduction in the hazard ratio for MACE at a
13 two-sided alpha of .05. So this was clearly a
14 superiority trial. The targeted number of major
15 adverse cardiac events was 1600. The investigators
16 assumed a 3 percent annual MACE rate in the control
17 group. And if you plug in the formula that Dr. Soukup
18 showed you earlier, you come up with roughly 53,000
19 patient years of exposure that you need.

20 Just briefly, to give you a sense of the
21 patients in the CRESCENDO trial, the mean age was 64;
22 36 percent were female. They were mostly Caucasian.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

274

1 The mean BMI was 33. Thirty-six percent had a history
2 of MI, 18 percent had a history of stroke. And
3 diabetes, hypertension, and hypercholesterolemia were
4 quite prevalent in this population.

5 In November of 2008, regulatory authorities
6 in Ireland, France, and Germany requested that all
7 clinical trials with rimonabant be stopped. And this
8 was due to concern about serious psychiatric adverse
9 reactions, most notably, completed suicides. So at
10 that time, CRESCENDO was terminated after a mean
11 exposure to study drug of 13.8 months. The plan to
12 minimum had been 33 months.

13 So I've shown you here the results from this
14 truncated trial really accumulate a little bit less
15 than half the target number of events. So you can see
16 that the incidence of MACE in the placebo group was 4
17 versus 3.9 in rimonabant. So again, based on these
18 truncated data, the hazard ratio for MACE was 0.97 with
19 a 95 percent confidence interval of 0.84 to 1.12.

20 This is simply showing you the same data as
21 Kaplan-Meier curves. You can see that at a little bit
22 beyond the first year, you see a slight separation of

1 the lines in favor of rimonabant. And interestingly
2 enough, the investigators postulated that you would see
3 no treatment effect during the first year, that it
4 would take at least that long to see these favorable
5 changes actually turn and reduce event rates, which is
6 something to keep in mind as we're talking about
7 interim analysis in cardiovascular outcome trials. If
8 most of the data is going to be accrued during the
9 first year and you don't really think you're going to
10 see a treatment effect, that may not be the wisest
11 course to follow.

12 Now, these are the Kaplan-Meier curves for
13 the two subgroups, those who entered the -- so again,
14 these are the Kaplan-Meier curves for the two
15 subgroups: the individuals who had overt CVD when they
16 entered the trial and those who were just at risk for
17 CVD, but did not have a history of heart disease.

18 You can see, in those who had overt CVD, the
19 hazard ratio, the point estimate was a little bit below
20 1 at .95, and the 95 percent confidence interval was
21 .80 to 1.13. And you clearly see a separation at one
22 year in favor of rimonabant. I think you lose this

1 here because the number of events just gets so small.
2 In contrast, you really don't see anything in this
3 lower-risk group. The hazard ratio is basically 1 with
4 a confidence interval of .79 to 1.35.

5 So if you really want to try to find a
6 treatment effect in a most robust manner, you'd be
7 better off sticking with this cohort of individuals and
8 not even bothering enrolling this group.

9 So let me move onto sibutramine in the SCOUT
10 trial. Sibutramine was a neuronal norepinephrine
11 serotonin reuptake inhibitor developed for the
12 treatment of obesity in the 1990s. At about 15
13 milligrams a day, it led to a placebo-subtracted weight
14 loss of about 4 percent. Sibutramine-induced weight
15 loss had a favorable effect on HDLC and triglycerides.
16 It had inconsistent effects on measures of glycemia,
17 and it caused placebo- subtracted increases in blood
18 pressure of 1 to 3 millimeters of mercury. And it
19 increased heart rate on average of 3 to 5 beats per
20 minute. The drug was approved for the treatment of
21 obesity by FDA in 1997.

22 The sibutramine cardiovascular outcomes, or

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

277

1 SCOUT trial, was a randomized, double-blind, placebo-
2 controlled study of about 10,000 subjects. The primary
3 endpoint was MACE, a composite here of CV death, non-
4 fatal MI, non-fatal stroke, and in this case,
5 resuscitated cardiac arrest. I still would refer to
6 this as strict MACE, resuscitated cardiac arrest.
7 There were not very many events. The trial began in
8 January of 2003 and was completed in March of 2009.

9 So briefly, the inclusion criteria was age
10 greater than 55, a BMI of 27 to 45, or you could have a
11 BMI of 25 to 26.9 if you had abdominal obesity. And
12 that was defined as an increase in waist circumference.

13 In terms of cardiac risk, you had to have
14 either a history of cardiovascular disease or type 2
15 diabetes with an additional risk factor, or you could
16 have both. So this led to three subgroups in terms of
17 cardiovascular risk at baseline. The highest risk
18 group were those with CVD plus diabetes; had some with
19 cardiovascular disease alone, did not have diabetes;
20 and then those with diabetes without a known history of
21 cardiovascular disease. And again, I'll show you
22 results by these three subgroups in a moment.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

278

1 This is a schematic. I just simply want to
2 make a couple of points, and we touched on this earlier
3 with comments that Dr. Bray made. So the first six
4 weeks of SCOUT, all study subjects received single-
5 blind sibutramine, 10 milligrams plus lifestyle
6 modification. During this six months, there was an
7 average weight loss of about 2.8 percent. And I do
8 believe that the blood pressure and pulse went down in
9 this group. And this is where they actually were
10 randomized to continue sibutramine or go on placebo.

11 So these reductions in weight and vital signs
12 really made it difficult to interpret the events that
13 occurred down here because, if you took it from this
14 point, is that really the baseline here, or is it
15 really baseline back here? And if it's back here,
16 there's only one group, and they're all getting
17 sibutramine. So it made it very difficult to interpret
18 the results. And if people could avoid these lead-ins,
19 I think they'd be better off.

20 The other point I wanted to make -- and we've
21 also touched on this -- is, like CRESCENDO, people
22 stayed on study drug during their randomization phase,

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

279

1 regardless of whether they lost weight. And if you
2 have a drug, particularly a sympathomimetic, you could
3 argue that if their blood pressure and pulse are okay
4 and they're not losing weight, they may well be
5 avoiding gaining weight. But some would argue that
6 these people, if they don't lose weight, should be
7 taken off the drug. So that's another issue that we'll
8 talk more about tomorrow.

9 So SCOUT had 80 percent power to detect 11.5
10 percent reduction and a hazard ratio for MACE at a two-
11 sided alpha of .05. Again, this was powered as a
12 superiority trial. The target number of events was a
13 little over 2,000. The investigators assumed a 7
14 percent annual MACE rate in the control group. Again,
15 applying Matt Soukup's equation, you come up with
16 approximately 31,000 patient years of exposure.

17 There was indeed a lower-than-expected
18 primary event rate during the first 15 months of SCOUT,
19 so this led to some changes in the protocol. They
20 restricted inclusion to subjects with a history of
21 cardiovascular disease and diabetes, assuming they
22 would have the highest event rate. And the follow-up

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

280

1 was extended from five years to six years. Quickly,
2 the demographics, the mean age was 63; 42 percent were
3 female, mostly Caucasian.

4 Throughout the course of the trial, about 40
5 percent of the subjects in each treatment group
6 discontinued drug prematurely, but the company did a
7 good job and the investigators did a good job of
8 collecting vital status and event data for the
9 individuals who went off study drug but remained in the
10 trial. So they had very good follow-up data for the
11 entire study cohort.

12 SCOUT was stopped after six years, and they
13 had accrued a little less than half of the originally
14 targeted primary events. The mean exposure to study
15 drug was 3 and a half years. Shown here are the
16 primary efficacy outcomes for the intention-to-treat
17 population. You can see that the incidence of MACE in
18 the placebo group was 10 percent, compared to 11.4
19 percent in sibutramine. That led to a point estimate
20 for the hazard ratio of 1.16, with a 95 percent
21 confidence interval of 1.03 to 1.31. So this excluded
22 risk above 31 percent. This increased risk was driven

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

281

1 by non-fatal MI and non- fatal stroke. You can see the
2 point estimates here.

3 Just to show you the Kaplan-Meier curves for
4 the primary outcome, again, you can see that the lines
5 begin to diverge around 18 months in favor of placebo.
6 I'm not aware that this was stopped specifically
7 because of harm, but I can't imagine the trial would
8 have gone on much longer, given these results.

9 So these are the MACE data for the three
10 cardiovascular subgroups. And remember, diabetes
11 alone, cardiovascular alone, and cardiovascular disease
12 plus diabetes. The hazard ratio of the point estimate
13 was 1 for the diabetes-alone group, 1.3 for the CV
14 alone, and 1.2 for the CV plus diabetes.

15 A lot of people looked at these numbers and
16 said, well, there's actually no evidence of any
17 increase in risk in this group with diabetes alone. A
18 lot of people felt that way. However, from a
19 statistical standpoint, these three treatment effects
20 did not differ significantly, as the interaction p
21 value was .56. And that even takes into account the
22 fact that most of these analyses have low power. So we

1 concluded that the treatment effects across these three
2 groups were similar.

3 Now, before I leave SCOUT, I want to make a
4 couple of comments about how the treatment effect or
5 the risk estimate can vary depending upon the
6 population you study, and it can vary depending on the
7 endpoint you use.

8 So I've shown you for SCOUT the hazard ratio
9 for MACE from the intention-to-treat population was
10 1.16. And this intention to treat includes all people
11 randomized, regardless of whether they're on study drug
12 or not. This would be akin to what Dr. Soukup called
13 the total time analysis, so on treatment plus off
14 treatment.

15 FDA did an analysis, which was restricted to
16 on treatment or on drug. Only those individuals were
17 on drug. The hazard ratio there, the point estimate
18 was
19 1.21.

20 The other point I want to make is you can get
21 a slightly different risk estimate depending on the
22 endpoint you use. Recall that with a strict MACE, the

1 hazard ratio is 1.16. When we looked at MACE plus
2 revascularization procedures from SCOUT, we saw that
3 the incidence in placebo group was 17.5. Incidence in
4 the sibutramine group was 18.9. So the hazard ratio
5 point estimate was 1.10, which was not statistically
6 significant.

7 So the point I want to make here is,
8 depending on the population that is analyzed and the
9 endpoint that is analyzed, you may see different
10 estimates of risk. And again, this is an issue we'll
11 get into tomorrow.

12 Just very quickly, I want to point out that
13 the subjects who took part in the two cardiovascular
14 outcomes trials, this one with rimonabant for
15 CRESCENDO, compared to the subjects who took part in
16 these phase 3 clinical trials for rimonabant. These
17 were diabetics. These were non-diabetics.

18 You'll notice that the outcomes trial
19 participants were much older than the typical phase 3
20 participants. And for the most part, there are fewer
21 females in the cardiovascular outcomes trial compared
22 to the typical phase 3 trials, pre-approval trials.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

284

1 You see the same thing with the SCOUT trial
2 versus the two phase 3 trials for the sibutramine
3 development program. SCOUT participants, 63 here, 54
4 and 43. Only 43 percent women were in the SCOUT trial,
5 versus 51 and 81 in the standard phase 3 trials.

6 So to summarize and conclude, CRESCENDO and
7 SCOUT were randomized, placebo-controlled clinical
8 trials designed to examine the effect of drug-induced
9 weight loss on risks for MACE. These were both
10 designed to superiority trials. They were powered to
11 detect 15 and 11.5 percent reductions, respectively, in
12 the hazard ratio for MACE. Sample sizes were over
13 18,000 for CRESCENDO and about 10,000 for SCOUT. And
14 they had to enroll subjects with and without
15 cardiovascular disease.

16 So compared with the typical phase 3 clinical
17 trials of sibutramine and rimonabant, the populations
18 enrolled in CRESCENDO and SCOUT were older, composed of
19 more males and type 2 diabetics, and included many more
20 subjects with a history of cardiovascular disease.
21 This is quite telling as well. The annual incidence
22 rate of MACE in the control groups from CRESCENDO and

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

285

1 SCOUT were 3 to 4 percent.

2 Now, we looked more recently at the MACE
3 event rate in some of the obesity drug applications
4 we've reviewed in the last couple of years. And in
5 that situation, the annual incidence rate of MACE in a
6 typical phase 3 clinical trial of recently reviewed
7 obesity drugs is less than 0.5 percent. So this gets
8 to one of our discussion points tomorrow, which is,
9 what is the value of enriching the standard population
10 with higher risk individuals in order to try to detect
11 a signal for adverse cardiac effects? And I'll leave
12 it at that.

13 DR. THOMAS: Thank you, Dr. Colman.

14 We now have our next speaker, Dr. Guettier.

15 DR. GUETTIER: Good afternoon. My name is
16 Jean- Mare Guettier. I'm an acting team leader for
17 diabetes in the Division of Metabolism and
18 Endocrinology Products. My talk this afternoon will
19 focus on evaluating cardiovascular risk for new drugs
20 being developed to treat type 2 diabetes. In the
21 background material, I will make no distinction between
22 the different types of diabetes since the information I

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

286

1 cover is applicable to almost all types. When I start
2 talking about the guidance, I will be referring solely
3 to drugs used for the treatment of type 2 diabetes.

4 I will start by providing basic background
5 information about diabetes and obesity. My intent with
6 this background material is to change the focus of the
7 discussion from obesity to diabetes. In the background
8 material, I will touch on many key issues specific to
9 diabetes drug development that were considered at the
10 time of the advisory committee meeting and for the
11 purpose of guidance development.

12 Since there is overlap between obesity and
13 diabetes, I thought I would start by presenting key
14 aspects of each disorders that are relevant in the
15 context of drug development. I would like to begin by
16 comparing the characteristics, features of these
17 disorders.

18 Obesity is a disorder characterized by an
19 excess of total body fat and associated with an
20 increased risk of concomitant diseases, disability, and
21 death. In contrast, diabetes is a disorder
22 predominantly characterized by abnormal glucose and

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

287

1 associated with complications that result specifically
2 from excess blood glucose, so that by the time an
3 individual meets the diagnostic criteria for type 2
4 diabetes, the patient has evidence of end-organ damage.

5 Obesity and diabetes are similar in that in
6 absolute terms, they are highly prevalent disorders.
7 Epidemiological data has shown that the rise in
8 prevalence of type 2 diabetes has followed in parallel
9 the rise in obesity prevalence.

10 You will note from this slide that the
11 proportion of the population affected by diabetes is
12 smaller than the proportion of individuals affected by
13 obesity. Subjects who are obese and have diabetes, by
14 definition, have one of the many complications of
15 obesity. Finally, since these diseases are highly
16 prevalent, small increases in relative risk of a common
17 disorder, such as cardiovascular disease, can have
18 broad public health repercussions.

19 Both illnesses are associated with multiple
20 clinical complications across many organ systems. We
21 have heard about the clinical impact of obesity this
22 morning. Acutely untreated diabetes causes symptoms

1 attributed to excess blood glucose. Chronically
2 elevated blood glucose levels, in turn, will impact the
3 microvasculature of the eye, the nerve, and kidney, and
4 could lead to loss of vision, loss of peripheral
5 sensation, and loss of kidney function.

6 Diabetes also impacts large vessels and
7 increases an individual's lifetime risk of developing
8 atherosclerotic cardiovascular disease. For both of
9 these disorders, it is logical to assume that if the
10 major pathobiological feature upstream of these
11 complications is treated, a broad array of clinical
12 outcomes could be affected.

13 Both disorders have an obvious upstream
14 pathobiologic target. The most specific and
15 predominant pathobiologic factor in obesity is excess
16 adiposity. In diabetes, the most predominant and
17 specific pathobiologic factor is excess glucose. New
18 drugs developed to treat those disorders target these
19 excesses with an aim to reduce the adverse clinical
20 outcomes associated with these diseases. I will come
21 back to this point later for diabetes.

22 The two diseases are similar in that they are

1 complex metabolic disorders. And although a specific
2 pathobiologic, metabolic abnormality predominates,
3 there are often multiple other concomitant
4 abnormalities that could contribute either directly or
5 through interactions to one or more of the adverse
6 clinical outcomes.

7 It is well-recognized, for example, that the
8 prevalence of both traditional and non-traditional
9 cardiovascular risk factors is high in subjects with
10 diabetes and obesity. These can contribute to
11 cardiovascular disease directly or can interact with
12 another factor, such as glucose in the case of
13 diabetes, to augment cardiovascular risk.

14 In this slide, I contrast the number of
15 current drug therapeutic options available in the
16 United States for the treatment of obesity and
17 diabetes. You've heard this afternoon about the
18 limited options available for obesity. Up until the
19 mid-1990s, the options for diabetes were limited to
20 insulin and sulfonylurea. Today, in contrast, a
21 physician treating a patient with type 2 diabetes can
22 select a medication from up to 11 therapeutic classes.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

290

1 This may appear as a large number, especially when
2 contrasted to the number of medications available to
3 treat obesity. But in reality, the choice could be
4 much more limited once factors such as disease stage,
5 tolerability, and contraindications in an individual
6 patient are taken into account.

7 Furthermore, it is well-recognized that the
8 underlying pathophysiology of type 2 diabetes is
9 progressive. Glycemic control in most individuals on
10 any individual therapy worsens over time, and
11 additional therapy to maintain glucose control is
12 needed, so choice is a good thing.

13 This morning, you heard the facts about
14 obesity. I will now present the facts about diabetes.
15 In terms of prevalence, diabetes affects about 26
16 million individuals or 1 in 12 persons in the United
17 States. The majority of these individuals have type 2
18 diabetes. Between one-half to one-third of diabetic
19 patients are older than 65 years old.

20 I stated before that the microvascular
21 complications of diabetes lead to many disabling
22 conditions in individual patients. In terms of public

1 health impact, these complications account for the fact
2 that diabetes is the leading cause of kidney failure,
3 non-traumatic lower limb amputation, and new case of
4 blindness in the United States.

5 With regards to heart disease, diabetes is a
6 leading cause of heart disease and cerebrovascular
7 disease. In fact, it has been estimated that a
8 diabetic individual's risk of heart disease and stroke
9 is two to four times that of a normal individual. This
10 suggests that subjects with diabetes are particularly
11 susceptible to cardiovascular disease.

12 In terms of mortality associated with
13 diabetes, we know that subjects with diabetes are two
14 to four times more likely to die from a cardiovascular
15 cause. Data from death certificates suggests that
16 cardiovascular disease accounts for two-thirds of
17 deaths due to diabetes. So patients with diabetes are
18 not only susceptible to cardiovascular disease but also
19 particularly susceptible to bad outcomes associated
20 with cardiovascular disease.

21 Based on the characteristics, features, and
22 known complications of diabetes, we can construct the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

292

1 following simple disease model. As I have stated
2 before, diabetes is a disorder of glucose metabolism,
3 which leads to excess blood glucose. In turn, this
4 results in the following adverse clinical outcomes. We
5 can reliably measure plasma glucose. And from
6 etymological studies, we know the thresholds for
7 various glycemic parameters that define glucose excess
8 and puts an individual at risk of these complications.

9 This model is useful because of its
10 simplicity, but like all models, oversimplifies the
11 pathophysiology of the disorder. First, it assumes
12 that all of the clinically important deleterious
13 effects that result from diabetes can be captured by
14 looking at excess glucose.

15 This assumption is valid for complications
16 which are more specifically linked to high glucose, in
17 this slide, the symptoms in the microvascular
18 complications. But for other complications, and in
19 particular for microvascular disease, the assumptions
20 that glucose captures all of the effect is not valid,
21 as the model ignores other traditional and non-
22 traditional risk factors for cardiovascular disease

1 highly prevalent in diabetes. These additional risk
2 factors may have direct impact on the outcome or may
3 interact with glucose to impact the health outcomes.

4 Finally, this model assumes that glucose
5 contributes equally to these outcomes and that the
6 influence glucose has on these outcomes over time is
7 constant.

8 I'm now going to start talking about the
9 therapeutics in diabetes. And in this slide, I
10 illustrate where drugs to treat diabetes fit in the
11 disease model. Currently, all new drugs to treat
12 diabetes are indicated to improve glycemic control, and
13 this is based on demonstrating a significant reduction
14 in the glycosylated hemoglobin product known as
15 hemoglobin A1c.

16 The therapeutic model, as presented here, is
17 the mirror image of the disease model. It assumes that
18 clinical benefit associated with the drug can be
19 captured by demonstrating a reduction in blood glucose.
20 This model is useful because innovative therapies can
21 reach patients more rapidly than if drugs were required
22 to demonstrate an effect on long-term health outcomes.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

294

1 This model, however, has shortcomings, and
2 these were discussed at the July 2008 advisory
3 committee meeting. Similar to the disease model, it
4 assumes that the totality of the drug effect can be
5 captured by looking at a single biomarker. We know
6 this is not the case, and we recognize that drugs can
7 have direct or indirect effects on these and other
8 clinical outcomes that could affect the overall risk-
9 benefit of the drug.

10 Despite the shortcomings of the previous
11 illustrated model, we know that lowering blood glucose
12 leads to important clinical benefits. First and
13 perhaps most obviously, lowering blood glucose has the
14 immediate benefit of ameliorating the symptoms and the
15 signs caused by hyperglycemia. Second, improving
16 glucose control using insulin in type 1 diabetes or
17 insulin and sulfonylurea in type 2 diabetes was shown
18 in two large pivotal, prospectively conducted
19 randomized control trials to reduce both the onset and
20 the progression of microvascular complications.

21 The results from the DCC trial carried out in
22 type 1 diabetes and the UKPDS trial carried out in type

1 2 diabetes patients suggests that improvement in
2 glucose control, captured by demonstrating differences
3 in hemoglobin A1c, can reliably predict improvement in
4 microvascular outcomes. Improvement in glucose
5 control, however, has not consistently been associated
6 with a reduction in macrovascular disease outcomes.

7 Evidence from the long-term follow-up of the
8 DCCT and UKPDS trials suggests that tight glucose
9 control early in the disease process could provide
10 cardiovascular benefit years after the intervention has
11 ceased and years after the between-group difference in
12 Hb1c has disappeared.

13 The ACCORD study, a study examining the
14 effect of aggressive glucose lowering on macrovascular
15 disease outcomes in a population of subjects who had
16 had diabetes for a median of 10 years and were at high
17 risk of recurring CVD was stopped early due to
18 increased mortality.

19 Two other trials, the ADVANCE and VADT
20 trials, also examining aggressive glucose lowering in
21 subjects with longstanding type 2 diabetes at risk of
22 cardiovascular disease, did not confirm the finding of

1 increased mortality and did not demonstrate improvement
2 in cardiovascular risk with tight glucose control.

3 So to recap, we know subjects with diabetes
4 are particularly vulnerable to cardiovascular disease.
5 Yet, robust data showing that improvement in glucose
6 control leads to beneficial cardiovascular outcomes is
7 lacking.

8 Another complicating factor is the potential
9 for some anti-diabetic drugs to directly contribute to
10 the cardiovascular disease burden. This possibility
11 was first suggested in the 1970s with tolbutamide, a
12 sulfonylurea used in the University Group Diabetes
13 Program study and more recently with widely publicized
14 examples of unapproved and approved therapeutics.

15 The role of these complex issues in informing
16 the risk-benefit assessment and regulatory requirements
17 of new drugs to treat diabetes were discussed at the
18 July 2008 advisory committee meeting.

19 In the next few slides, I'm going to give you
20 an idea of what a typical late-stage clinical
21 development program for an agent seeking an indication
22 for type 2 diabetes, prior to the implementation of the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

297

1 cardiovascular safety guidance.

2 The clinical benefit, as stated before, was
3 demonstrated by showing an improvement in glucose
4 control using hemoglobin A1C to measure glycemia. To
5 establish clinical efficacy, the sponsor usually
6 carried out one or two phase 2 studies. These studies
7 were typically randomized, double-blind, placebo-
8 controlled, dose- ranging studies comparing the
9 investigational agent to placebo.

10 The population enrolled in these studies were
11 relatively healthy subjects with type 2 diabetes,
12 usually on no treatment or randomized after an adequate
13 washout of their pre-trial therapy. Efficacy was
14 established by demonstrating superior glycemic control
15 at the end of 12 weeks, compared to placebo, by
16 examining the change from baseline in hemoglobin A1c
17 between a dosing group and placebo.

18 To confirm clinical efficacy, the sponsor
19 usually carried out five to six phase 3 studies. These
20 studies were typically randomized and double blind, and
21 examined two doses of the investigational agent that
22 were found in the phase 2 studies. In these trials,

1 the investigational agent was used as monotherapy or
2 was added to existing background therapy, and compared
3 against placebo to establish superiority, or compared
4 to an active drug to establish non-inferiority.

5 Efficacy was demonstrated at the end of six months,
6 usually using an endpoint variable similar to the one
7 used in phase 2 studies.

8 Studies were then typically extended past the
9 primary efficacy endpoint to obtain additional exposure
10 and safety data. The extensions prior to the
11 cardiovascular guidance were, for the most part,
12 voluntary and uncontrolled.

13 In terms of recommended exposure to the
14 investigational agent, sponsors were asked to have at
15 least 2500 subjects exposed to the investigational
16 product in their phase 2 and phase 3 studies, with
17 between 1300 to 1500 subjects exposed for at least one
18 year and 300 to 500 subjects exposed for at least a
19 year and a half.

20 The bulk of the safety data was obtained from
21 the six-month confirmatory studies and some from the
22 mostly voluntary, uncontrolled extension of these

1 studies. The analyses of safety were usually
2 descriptive. For cardiovascular risk specifically,
3 there was no requirement to standardize the definition
4 and to prospectively capture or adjudicate
5 cardiovascular safety endpoints.

6 These analyses were neither designed nor
7 powered to exclude a specific amount of excess risk.
8 If results from non-clinical or clinical studies
9 suggested an increased risk, the sponsor was asked to
10 carry out prospective studies to evaluate this
11 potential risk, either pre- or post-marketing.

12 In this example, I show the exposure in blue,
13 participant baseline characteristics in yellow, and
14 cardiovascular safety analysis in white for two
15 programs that had completed development before issuance
16 of the guidance.

17 As you recalled, we asked that at least 2500
18 subjects be exposed to investigational drug in the
19 phase 2/3 program. These two programs met the minimum
20 recommended exposure. You can see that at least for
21 one of these programs, the number exposed for one year
22 was below the recommended exposure. From the baseline

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

300

1 characteristics shown here, you can tell that the
2 majority of subjects exposed were not at high risk of
3 developing cardiovascular disease.

4 MACE stands for major adverse cardiovascular
5 events, as you've heard before. And MACE is a
6 composite endpoint group in cardiovascular death, non-
7 fatal myocardial infarction, and non-fatal stroke.
8 MACE is shown here in quotes because, in these two
9 programs, no standard prospective definition, capture,
10 or adjudication of these endpoints were implemented.

11 The analysis of cardiovascular safety was
12 therefore done retrospectively by acquiring the adverse
13 event database for terms representative of the
14 individual component of MACE. Post hoc adjudication of
15 these events was not possible. In addition to the
16 limitation of this data, you can also see that the
17 number of MACE events and the rate of MACE events was
18 low for a population with diabetes and would have been
19 even lower if adjudication had occurred in both
20 programs.

21 These two examples illustrate the point that
22 in most diabetes drug development programs prior to the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

301

1 guidance, subjects enrolled in the studies were not at
2 high risk of cardiovascular events and that robust
3 assessment of cardiovascular risk before marketing was
4 not possible.

5 This leads us to the July 2008 advisory
6 committee meeting. Many of the topics presented in my
7 background slides were considered at the 2008 advisory
8 committee meeting, and the panel members were asked to
9 weigh these issues in their discussion and
10 deliberations, surrounding the need for cardiovascular
11 risk assessment in the context of diabetes drug
12 development. The committee members -- many of them are
13 here today -- included endocrinologists,
14 diabetologists, cardiologists, statisticians, and drug
15 safety experts.

16 The following specific issues were discussed.
17 First, should there be an additional requirement to
18 assess cardiovascular risk in type 2 diabetes drug
19 development programs? And if so, what type of
20 assessment should be carried out? Would a meta-
21 analysis of the standard diabetes program be a valid
22 assessment, or would a dedicated cardiovascular

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

302

1 outcomes trial be needed?

2 Second, when should the assessment occur?

3 Should it or pre-approval or post-approval? Third,
4 which drugs should be required to undergo the
5 assessment, all drugs or only those drugs with a safety
6 signal? And fourth, would the new assessment apply
7 only to the new drugs or also to the currently marketed
8 drugs?

9 With regard to the type of assessment, the
10 following specific points were discussed. Should the
11 primary objective of the trial be to demonstrate
12 superiority or to exclude excess risk? If the
13 objective of the trial is to exclude excess risk, what
14 constitutes an acceptable level of risk in the context
15 of the expected benefit afforded by glycemic control?
16 What should the primary endpoint be, MACE or MACE and
17 other factors? What type of patients should be
18 included in the assessment, those most at risk or
19 another population of patients with diabetes?

20 In light of the uncharacterized
21 cardiovascular safety profile of older anti-diabetic
22 agents and the expected glucose deterioration with

1 placebo, what would the most appropriate comparator be,
2 placebo or an active comparator?

3 In these trials, since these trials would be
4 long-term trials, how should the expected glucose
5 deterioration be handled to avoid confounding and to
6 preserve the internal validity of the trial? Who and
7 how should traditional cardiovascular risk factors be
8 managed in these trials? Should these be prespecified
9 in the protocol or handled as per local standard of
10 care? And finally, how should cardiovascular endpoints
11 be handled?

12 At the end of two days of presentation and
13 deliberation, the panel voted on the following
14 question, which I will now read. It should be assumed
15 that an anti-diabetic therapy with a concerning
16 cardiovascular safety signal during phase 2/3
17 development will be required to conduct a long-term
18 cardiovascular trial.

19 For those drugs or biologics without such a
20 signal, should there be a requirement to conduct a
21 long- term cardiovascular trial or to provide other
22 equivalent evidence to rule out an unacceptable

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

304

1 cardiovascular risk? Fourteen panel members voted yes
2 and 2 panel members voted no.

3 The original question ended at the end of the
4 bolded black font. The panel re-worded the question to
5 include the bolded green highlight because the majority
6 of the panel members did not want to commit to
7 recommending a single long-term cardiovascular outcomes
8 trial, as was suggested by the bold statement in black.

9 Panel members who voted yes were then asked
10 to discuss when in drug development these studies
11 should be conducted. The majority of panelists voted
12 to start the study during the pre-approval period and
13 complete the study in the post-approval period.

14 I will now go over the recommendations that
15 were issued in the form of a guidance document after
16 careful consideration of the advisory panel
17 recommendation.

18 The guidance was published in December 2008.
19 First, the guidance reaffirms that hemoglobin A1c is
20 the primary efficacy endpoint for glucose reduction.
21 It recognizes that patients with diabetes are
22 particularly predisposed to developing cardiovascular

1 disease. Because of this fact, it asks the sponsor to
2 demonstrate that new therapies for type 2 diabetes do
3 not increase cardiovascular risk to a level that would
4 be considered unacceptable.

5 The guidance does not advocate for or against
6 a specific type of study. It recommends that the
7 sponsor establish an independent, blinded
8 cardiovascular endpoint committee to prospectively
9 adjudicate major adverse cardiovascular events during
10 phase 2 and 3 clinical trials.

11 It also recommends that sponsors design their
12 phase 2 and 3 clinical trials in a way to allow
13 performance of a prespecified meta-analysis of major
14 adverse cardiovascular events. This entails
15 prospectively the finding of the event of interest and
16 standardizing the capture and adjudication of these
17 events.

18 It recommends that patients at an increased
19 risk of cardiovascular disease be enrolled to obtain
20 sufficient endpoints to allow a meaningful estimate of
21 the risk. And in particular, it recommends enrolling
22 elderly individuals and those with renal impairments,

1 two subgroups that were underrepresented prior to the
2 guidance. It asks sponsor to provide a protocol
3 describing the statistical methods for the proposed
4 meta- analysis of all placebo-controlled trials, add-on
5 trials, and active comparator trials.

6 In terms of quantifying excess cardiovascular
7 risk, the guidance recommends that risk be estimated by
8 comparing the incidence of major cardiovascular events
9 in the investigational agent to that of the control
10 group.

11 Schematically, the rate of cardiovascular
12 events is compared to the rate of cardiovascular events
13 in the comparator. From the incidence rate ratio or
14 the hazard ratio, the point estimate of risk is
15 derived, and the uncertainty around the risk is
16 determined. These statistics are then compared to a
17 level of no increased risk, depicted here in the dotted
18 blue line, and to the threshold where margin use
19 defined an unacceptable level of risk, depicted here in
20 the dotted red line.

21 You've heard Dr. Soukup's talk this afternoon
22 on design of studies aimed at evaluating risk

1 endpoints. With regard specifically to the diabetes
2 guidance, sponsors are asked to test two sets of
3 hypotheses. The null hypothesis for the first set is
4 that the drug is associated with a relative
5 cardiovascular risk increase of 80 percent or greater,
6 depicted here by a hazard ratio of 1.8. The null
7 hypothesis for the second set is that the drug is
8 associated with a relative risk increase of greater
9 than 30 percent, depicted here by a hazard ratio of 1.3
10 or greater.

11 Now, the goal is to test each null hypothesis
12 and to reject both. The testing can occur
13 simultaneously or sequentially. And the probability of
14 falsely rejecting the null is set at 2.5 percent for
15 each of the null hypotheses.

16 This table summarizes how the concepts that
17 were presented in the two previous slides are applied
18 for the purpose of regulatory decision making. If the
19 evidence provided at the time of the NDA is unable to
20 exclude an 80 percent relative increase in
21 cardiovascular risk, that is, if the upper bound of the
22 95 percent confidence interval, appropriately adjusted

1 for multiplicity, exceeds 1.8, then the estimated
2 increased risk is "unacceptable." By "unacceptable,"
3 we mean that the residual uncertainty around the risk
4 is too high and not outweighed by the potential benefit
5 afforded by improved glycemic control and, therefore,
6 is inadequate to support drug approval.

7 If, on the other hand, an 80 percent relative
8 increase in cardiovascular risk is excluded, but a 30
9 percent relative increased risk is not, and the point
10 estimate of the risk is reassuring, the drug has
11 satisfied the cardiovascular safety requirements for
12 the purpose of marketing. But additional data post-
13 marketing are needed to rule out a 30 percent increased
14 risk.

15 Finally, if the evidence in the definitive
16 analysis excludes a 30 percent relative increase in
17 cardiovascular risk, that is, if the upper bound of the
18 appropriately adjusted 95 percent confidence interval
19 does not exceed 1.3, we consider that the residual risk
20 does not outweigh the glycemic benefit provided by the
21 drug and would not require additional post-marketing
22 studies.

1 The two-tiered approach was selected to allow
2 marketing of a product after some reassurance of a
3 product's safety, cardiovascular safety, and to require
4 that additional assurance of cardiovascular safety be
5 provided after marketing. This approach aimed to
6 balance the need for adequate cardiovascular safety
7 assessments with the need to make new therapies for
8 diabetes available. The additional uncertainty at
9 approval, again, is tolerated because in light of a
10 reassuring point estimate of risk, it is felt that the
11 risk is not outweighed by the benefit provided by
12 glycemic control.

13 I'm going to talk a little bit more about why
14 specifically the margin of 1.8 was selected as the
15 first margin to test. Feasibility had an important
16 role to play in this decision. Demanding that a
17 relative risk of 30 percent be definitively ruled out
18 pre-approval would have significantly delayed
19 availability of new drugs.

20 Indeed, to be able to rule out an excess
21 relative risk of 30 percent with 90 percent power, you
22 would need approximately 615 events. This number of

1 events is based on the assumption that the true
2 relative risk is 1, and that a 1 to 1 randomization
3 scheme and a 1-tailed alpha error of 2.5 is used.

4 Six hundred and fifty events is at least one
5 order of magnitude larger than the number of events
6 seen in a development program prior to the guidance.
7 Requiring that drugs exclude a relative risk increase
8 of 1.8 was thought to be feasible. Using the same
9 assumptions, sponsors could exclude this risk with
10 approximately 125 events. This represented a number
11 three to five times larger than the number of events
12 seen in programs before the guidance.

13 Post-approval, the sponsors were asked to
14 definitively exclude a relative risk of 30 percent
15 above comparator. Some of the reasons for selecting
16 this margin are discussed in this slide. Several
17 margins were considered, namely 1.2, 1.3, and 1.4.
18 These represent relative risk increases of 20, 30, and
19 40 percent. Requiring that sponsors exclude a margin of
20 1.2 would have substantially increased the size and/or
21 the duration of diabetes programs.

22 In this scenario, 1300 events would have been

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

311

1 required to rule out 1.2, again, using the same
2 assumptions as in the previous slide. This number of
3 events is more than twice the number of events needed
4 to rule out 1.3. And assuming a 2 to 4 percent per-
5 year event rate, this would require that 10,000 to
6 20,000 individual patients be followed for up to three
7 years. 1.4 was also considered because at the time of
8 the advisory committee meeting, the discussion around
9 the rosiglitazone point estimate of 1.4 was considered
10 to be excessive.

11 Satisfying the requirement for 1.3 was
12 considered feasible in terms of additional data
13 required post-approval and had been suggested as a
14 valid margin in another setting where excess
15 cardiovascular risk was to be ruled out.

16 The guidance was issued in late 2008. In the
17 next few slides, I briefly discuss how recommendations
18 from the guidance have been implemented across diabetes
19 drug development programs. Again, the guidance
20 provides flexibility with regards to both the type of
21 studies and the statistical considerations that can be
22 used to evaluate cardiovascular risk in diabetes

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

312

1 programs. For example, the sponsor could carry out a
2 prospectively- planned meta-analysis of phase 2 and 3
3 trials or a dedicated cardiovascular outcomes trial, or
4 a combination of both types of studies to meet the
5 requirements. Thus far, more than 20 plans have been
6 submitted and reviewed, and each of them differ.

7 We have seen the following designs. Some
8 sponsors propose to perform a prospectively-planned
9 meta- analysis of all phase 2 and phase 3 trials
10 carried out in higher-risk individuals. Other sponsors
11 propose to actually pool the results from all phase 2
12 and 3 studies with the results from an ongoing
13 cardiovascular outcomes trial. Yet others have
14 proposed to carry out a single dedicated study in high-
15 risk patients.

16 All the plans mentioned until now are
17 designed to rule out excess risk. We have also seen
18 several proposals designed to demonstrate
19 cardiovascular benefit using large, dedicated
20 cardiovascular studies. By looking at all these
21 proposals, it appears that all sponsors have planned or
22 will have to conduct a dedicated cardiovascular safety

1 trial to exclude a relative risk increase of 1.3.

2 All the plans have the following common
3 design features. Assessment of cardiovascular risk is
4 prospectively implemented. Selection criteria aims to
5 include individuals at higher risk of cardiovascular
6 disease. Duration of exposure is increased through the
7 use of controlled, involuntary extensions. The capture
8 and definition of cardiovascular endpoints are
9 standardized. MACE or MACE plus hospitalization for
10 unstable angina is the primary endpoint. Events of
11 interest are adjudicated by a blinded, independent
12 clinical endpoint committee.

13 Finally, I'd like to conclude by contrasting
14 programs that filed for new drug applications before
15 and after the guidance implementation. This table
16 illustrates the impact the guidance has had in terms of
17 additional exposure requirements. Since the guidance
18 is relatively new, no anti-diabetic drug has, to date,
19 definitively excluded a hazard ratio of 1.3.

20 The two drugs shown here have met the first
21 requirement of the guidance, and these are drugs C and
22 D. I contrast these two programs with those two shown

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

314

1 in an earlier slide. The data shown is approximate,
2 since it is inherently difficult to compare across
3 distinct programs.

4 You see from this slide that the total number
5 of subjects exposed to investigational drug in phase 2
6 and 3 has increased by about 2,000 individuals, and the
7 total exposure in patient years has, on average,
8 increased. Although not shown here, the increase has
9 been driven in some part by routine use of controlled,
10 blinded safety extension of phase 3 studies.

11 With regards to sociodemographic
12 characteristics, sponsors are now actively recruiting
13 older individuals, and this is reflected in the slight
14 increase in the proportion of individuals who are 65
15 years old or older. Mean diabetes duration for
16 enrollees may have increased slightly. Perhaps not
17 surprising, the proportion of subjects with a history
18 of atherosclerotic cardiovascular disease enrolled in
19 these diabetes programs has increased by three- to
20 eightfold. The proportion of individuals with renal
21 impairment, hypertension, dyslipidemia, and high
22 Framingham risk scores, although not shown here, has

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

315

1 also increased dramatically. So exposure of higher-
2 risk individuals in development programs for diabetes
3 is now common.

4 What you can also see is that at the time of
5 a new drug application filing, cardiovascular safety
6 assessment of the drug is based on a larger number of
7 events. What you cannot appreciate from this slide is
8 that the MACE events are defined and captured in a
9 standard fashion across all trials in the program, but
10 these are prospectively and blindly adjudicated, and
11 that the analysis of the risk is preplanned and
12 adequately powered, yielding a more robust estimate of
13 the risk.

14 Finally, it is important to keep in mind that
15 this table represents only the first of two steps for
16 cardiovascular safety assessment and that sponsors who
17 meet 1.8 are required to continue their preplanned
18 trial until they rule out 1.3.

19 I'd like to conclude my talk by acknowledging
20 the people that helped in the presentation. Thank you.

21 DR. THOMAS: Thank you for your presentation.

22 We'll now take questions for Dr. Colman and

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

316

1 Dr. Guettier. And at the end of that, with the
2 remaining time, we'll take questions for the three
3 speakers who will be leaving today.

4 Dr. Hiatt?

5 DR. HIATT: The first question is for Dr.
6 Colman on your slide 23, the subgroup analysis from
7 SCOUT. This created some discussion at the time of the
8 meeting. One perspective was, well, we would never
9 give this drug to people with cardiovascular disease,
10 so the whole thing is irrelevant. People without these
11 cardiovascular risk factors would never have a problem.
12 But obviously they're stuck because you had to get
13 event rates up to a point where you could measure them.

14 So then you play the game of sort of higher
15 versus lower risk within these three high-risk
16 subgroups. And the patients with diabetes only had the
17 lowest risk of events, and those with the combination
18 had the highest.

19 If you look at the upper bound on the lowest
20 and the highest groups, they're pretty much identical,
21 1.3 something. And so playing that argument, you'd
22 say, well, the amount of risk excluded is the same; and

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

317

1 therefore there is no distinguishing between low- and
2 high-risk patients. And the interaction term was not
3 significant. Although sometimes, I think the absence
4 of a statistically significant interaction term could
5 be misleading, there could actually still be something
6 there. But then the point estimates look a little
7 different, don't they? I mean, 1 is truly 1.00 and the
8 other is 1.12, roughly.

9 So my first question is, how do you interpret
10 that? I know at the time we interpreted that as the
11 risk is really the same across the high- and low-risk
12 subgroups, but one might argue differently.

13 DR. COLMAN: I think, in the context of the
14 overall risk-benefit profile of the drug, and for those
15 of you who were at the advisory committee where we
16 discussed the SCOUT trial and the other sibutramine
17 data, certainly this raised some uncertainty about its
18 cardiovascular safety, even in those folks who did not
19 have a history of cardiovascular disease.

20 The other side of the coin, my recollection
21 is the sponsor was unable to provide adequate data to
22 suggest that the drug had non-cardiovascular benefits

1 that might outweigh this risk. So on a global risk-
2 benefit equation, I think that was part of the
3 thinking.

4 DR. HIATT: So it's easier in a situation
5 where the overall risk is increased definitively, but
6 if we're going to be wrestling with the fact that, for
7 obesity drugs, the event rate is around .5 percent per
8 year, the only way to meaningfully conduct a study
9 would be to enrich the populations, as have been done
10 here. And what you showed is that the demographics
11 shift. So in the primary populations, there are more
12 women than men, but that shifts when you put in people
13 with underlying cardiovascular disease.

14 So it still begs the question, if that's the
15 only strategy to get enough events to make some
16 decision, are you actually studying the same thing as
17 you would be in the intended-use population?

18 DR. COLMAN: Well, I don't want to speak for
19 anyone, but obviously, we may be able to find a middle
20 course where we're not going to be studying people.
21 And this obviously would apply to drugs that have
22 sympathomimetic effects. Some are stronger than

1 others. But we would certainly want to get, at a
2 minimum, the annual MACE event rate above 1.
3 Otherwise, it just wouldn't be feasible in terms of
4 numbers and duration.

5 DR. HIATT: Right, right.

6 DR. COLMAN: So I think we would all have to
7 come to an agreement that compared to the normal people
8 in the phase 3 trials who tend to be women in their 40s
9 without a history of cardiovascular disease, if you
10 want to do a cardiovascular outcomes trial, you're
11 going to have to enrich them with some high-risk
12 people.

13 DR. HIATT: Yes. My second question is on
14 the diabetes guidance. So in obesity drugs, placebo
15 control is the only, I think, way to go because there
16 is no active comparator one would really entertain.
17 But in diabetes drugs, there clearly is. And the
18 question about the safety of any diabetes drug except
19 metformin is kind of out there.

20 So I remember looking at the liraglutide
21 data. There were several trials that were placebo-
22 controlled, several that were active-controlled. And

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

320

1 if you're trying to exclude risk and your active
2 comparator has risk, then excluding risk from an active
3 comparator like that may be falsely reassuring. I was
4 always puzzled by how that was managed with the
5 diabetes guidance. I suppose it doesn't directly
6 impact our thinking today.

7 DR. GUETTIER: So I can speak for the
8 diabetes guidance. We don't make any specific
9 recommendation as to what the appropriate comparator is
10 for the trials, but we do review sponsors' planned
11 trials for all these nuances.

12 I think that if we saw a drug that claimed
13 that they met the guidance requirement based on what
14 you suggested, a drug that could have a potential
15 cardiovascular harm or where the cardiovascular harm is
16 unknown, we would take that into our consideration and
17 our review.

18 DR. HIATT: So if they said rosiglitazone was
19 my active comparator and looked pretty good, you
20 wouldn't do that.

21 DR. GUETTIER: I think, also, that goes with
22 some of the endpoints. Some sponsors have proposed

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

321

1 adding hospitalization for heart failure. Again, a lot
2 of these programs are now doing long-term
3 cardiovascular outcomes studies where, usually the drug
4 is started. Two drugs are compared and then there is
5 additional therapy as the glycemic benefit wears off.
6 So we're usually recommending that sponsors do a
7 placebo-controlled trial, and then they have rescue
8 criteria in both arms.

9 DR. THOMAS: Dr. Parks?

10 DR. PARKS: So clearly we would not accept an
11 active control of rosiglitazone or an active control
12 where there is some concern of cardiovascular safety.
13 But we acknowledge that therapies that got to market
14 before the diabetes guidance, we don't have clear
15 evidence of the cardiovascular safety profile as we're
16 expecting for a lot of the products coming in now. But
17 there's also a condition that we can't all of a sudden
18 say people cannot be treated for their diabetes.

19 So what we are looking for is, there's a
20 standard of care and the background there, that all
21 diabetic patients are now accepting to be able to
22 achieve glycemic control, because, as Dr. Guettier

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

322

1 mentioned, we accept that glycemic control in diabetics
2 is an important aspect of disease management.

3 So that's why while we say placebo control,
4 it's actually placebo on to standard of care. And for
5 the most part, most of these trials are coming in with
6 fairly similar standard of care based on many different
7 medical organizations that share a similar
8 recommendation. Metformin is usually your first-line
9 therapy. There's some debate in terms of what would be
10 your next best, but for the most part, they're fairly
11 comparable.

12 DR. THOMAS: Dr. Temple?

13 DR. TEMPLE: Mary, even if you -- or either
14 of you -- say that it's nominally placebo-controlled
15 trials, if you have to achieve similar glucose control
16 in both groups, aren't you, de facto, always comparing?
17 Doesn't it really have elements at least of an active
18 control in a large fraction of the patients, whatever
19 you thought you randomized to?

20 DR. PARKS: So what you're saying here is
21 that if it's a placebo control on a background standard
22 of care, they all have to achieve some similar goals

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

323

1 for glycemic control, based on the practice of medicine
2 in the different regions?

3 DR. TEMPLE: Right. And the placebo group
4 will get some extra.

5 DR. PARKS: Yes. And I think it's a little
6 early for us to see how the differential effects of the
7 investigational arm versus the control arm will be with
8 respect to glycemic control.

9 I think the best example that we have right
10 now would have to come from PROactive, because that was
11 a placebo-controlled trial, and it certainly was set up
12 so that both treatment groups had to be managed for all
13 their risk factors for the different regions, the
14 standard of care for the different regions. But in the
15 end, it was noted that in the placebo group, there was
16 less of a -- or there was better glycemic control in
17 the active control group than placebo. It's not to say
18 that they were necessarily horrible, but there was a
19 slight difference between the two.

20 DR. TEMPLE: Would that worry you? Would
21 that make you worry about the validity of the trial? I
22 know we've never shown that better control does any

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

324

1 good, but if the control is better in the treated group
2 than in the control group, that at least seems a little
3 troublesome.

4 DR. PARKS: That would clearly have to be
5 part of the review. I think that what we're seeing
6 here with the different algorithms for managing to goal
7 is that one may see is much more addition of other
8 therapies in the control group, including possibly
9 insulin, than the investigational arm.

10 DR. THOMAS: Dr. Cooper?

11 DR. COOPER: Dr. Colman, I have a question
12 for you. And this relates really to sort of thinking
13 about the mechanism for the increased risk that we see.
14 So in the background information that we received on
15 page 11, it described that in the sibutramine trial,
16 there was an increase in heart rate and an increase in
17 blood pressure relative to placebo.

18 Help me, if you will, understand a little bit
19 more about what that mechanism might be for that drug.
20 And then, if you can, help us as we think more broadly
21 tomorrow about how we understand the adverse
22 cardiovascular effects for these obesity drugs. How do

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

325

1 we begin to think through where mechanism might play a
2 role? For example, the three examples we've gotten
3 today, there's been valve effects. There's been
4 neuropsychiatric effects that have been adverse effects
5 that have led to changes in marketing.

6 So is that an important thing that we should
7 include in our equation? And what recommendations
8 would you have for us as we begin to think through this
9 tomorrow?

10 DR. COLMAN: I think the way we structure the
11 discussion points, one says, basically, for a drug that
12 has a signal, you can assume that that will be required
13 to do a cardiovascular outcomes trial. And then we ask
14 questions about the specific designs of that trial.

15 So we aren't necessarily asking the committee
16 to discuss what might be a signal, what might not be a
17 signal, how high does the LDL have to be to be a
18 signal, how high does the blood pressure have to be to
19 be a signal. We thought it would be more appropriate
20 if we simply said, look, we made the decision. This is
21 the signal. So they're going to need to do the trial.
22 Please give us some input on the design aspects of the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

326

1 trial.

2 DR. THOMAS: Dr. Seely?

3 DR. SEELY: I think Dr. Parks partially
4 answered this, but I just wanted to be sure. So on
5 slide 22, in the 2008 advisory committee meeting, was
6 the recommendation by the committee that the
7 cardiovascular assessment for the anti-diabetic drugs
8 only applies to new drugs, and was that the FDA
9 decision?

10 DR. PARKS: That is correct. The December
11 2008 guidance is specific to new therapies to treat
12 type 2 diabetes.

13 DR. THOMAS: Dr. Konstam?

14 DR. KONSTAM: Yes. Thanks. I wanted to
15 maybe just make sure we're all on the same wavelength
16 about what the upper boundaries really mean and what
17 they don't mean. And specifically, I guess one simple
18 way to put it is, are they sufficient, or necessary, or
19 both? And what I mean by that is that -- and I note
20 that in your slide about it -- by the way, it would be
21 worth having the SCOUT study up there because I think
22 it's illustrative of this.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

327

1 In the slide that you had, where you talked
2 about the 1.8 and 1.3, you had an asterisk that said
3 something on the bottom. It said something about
4 assuming an OK point estimate.

5 DR. PROSCHAN: Reassuring

6 DR. KONSTAM: Reassuring. Okay. And I know
7 from comments I've heard from sponsors and maybe even
8 from panelists, there's the assumption that if you meet
9 that 1.8, you're good to go, regardless of what that
10 point estimate is.

11 So maybe we need some clarity about that
12 because, for example, in the SCOUT example where the
13 drug was pulled off the market, the upper boundary, if
14 I have it right, was 1.34 or something. And one way,
15 you could have easily gotten that down by just keeping
16 going, and getting more events, and narrowing it, and
17 you know the 1.7 is exactly right there for you. You
18 beat the 1.3.

19 So can you comment about what the implication
20 would be if you have a 1.7 upper boundary, but your
21 point estimate is 1.15? How are we to interpret that?

22 DR. GUETTIER: So these are very good

1 comments. I think, yes, we thought about it. And
2 certainly, if we were reviewing an application where
3 the point estimate of the risk was 1.7, but the sponsor
4 actually met the 1.8 and did so by, just as you
5 suggested, increasing the number of events to narrow
6 the noise around the point estimate, we would not
7 consider that a reassuring point estimate.

8 Now, we don't specifically say what a
9 reassuring point estimate is, and that's because
10 usually it's a review issue. And it also depends on
11 how much glycemic benefit the drug has in terms of
12 weighing the risk and benefit.

13 DR. KONSTAM: Yes. I think it might be worth
14 expanding just a little bit on this because, as you
15 pointed out, 1.8 is a big number. Right? I mean, we
16 don't really want to approve drugs that have a 70
17 percent increase in mortality. We're just striking a
18 compromise, and I think you talked about that very
19 nicely. But if, on that, during the NDA, your point
20 estimate actually is 1.1 and your upper boundary is
21 1.7, to me, that would not be an attractive drug to
22 approve. Okay? And I just wonder whether you resonate

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

329

1 with that and that makes a lot of sense.

2 DR. GUETTIER: So I guess we would look at
3 the lower boundary as well. All of this is based on
4 the uncertainty around the point estimate. And so the
5 recommendations are basically, the first interim
6 analysis is done on a small number of events, and it's
7 sort of presumed that the uncertainty around the risk
8 is large at that point.

9 Maybe, Mary, you want to answer this
10 question. But I think that if the sponsor showed that
11 the point estimate was 1.1 and that the margin was less
12 than the upper bound of the 95 confidence interval, was
13 lower than 1.8, the lower bound was across the 1, at
14 that point, we would say we don't have enough data, and
15 we would wait for the definitive study to be done to
16 actually make a final decision on the risk.

17 But Mary can answer that.

18 DR. THOMAS: Dr. Parks?

19 DR. PARKS: So Dr. Konstam, what you're
20 bringing up here are all the different -- I don't want
21 to call it hypothetical situations, but these are all
22 things we're going to have to grapple with when these

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

330

1 data come in. I also want to emphasize that when we
2 look at these NDAs, we're not looking at only for
3 cardiovascular safety. So when Dr. Kaul had mentioned
4 earlier that they make 1.8 or they make 1.3, are they
5 good to go, even if they make it and their point
6 estimate is right on 1 or even below 1, we look at
7 other things as well. So 1.1 or 1.0 and making 1.8 or
8 1.3 is not the only thing we look at.

9 In terms of what we have told companies
10 specifically in guidance, we do state regardless of the
11 method use, sponsor should consider the entire range of
12 possible increased risk consistent with a confidence
13 interval and a point estimate of the risk increase.

14 For example, it would not be reassuring to
15 find a point estimate of 1.5, even if the 95 percent
16 upper bound was less than 1.8. Clearly, that's higher
17 than 1.1, but that is to relay the message here that
18 it's not just a matter of meeting an upper bound. We
19 look at all aspects of the statistical finding, the
20 point estimate, the lower bound, and the upper bound,
21 and the overall benefit-risk profile of the product.

22 DR. KONSTAM: I guess just one final comment

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

331

1 about that. I think I'm reassured because what I guess
2 I'm hearing -- and maybe it ought to be really clear to
3 sponsors and everybody else -- is that the 1.8 is
4 necessary but not sufficient. Right? And that's the
5 bottom line. But the only editorial comment I'd make
6 is that if I'm on a panel and I see a 1.2 point
7 estimate or a 1.15 point estimate, I'd be very
8 reluctant to approve the drug.

9 DR. THOMAS: Dr. Temple?

10 DR. TEMPLE: Marv, the only way to do what
11 you want at that stage is to essentially demand that
12 the drugs be likely to be superior to the control.
13 Otherwise, just as a random matter, they're going to be
14 .9, 1.1, at this stage. Remember, this is the early
15 stage.

16 DR. KONSTAM: Right.

17 DR. TEMPLE: So you have limited data.
18 There's no way to guarantee it's going to be below 1.

19 DR. KONSTAM: Sure, sure. But the basic
20 approach to safety is to be conservative. Okay? And
21 if in the NDA data you have a worrisome mortality
22 signal, then I think the usual approach to that would

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

332

1 be not to approve that, because you have a worrisome
2 signal and you'd like more data to prove that that
3 signal is wrong. I mean, that'd be the usual approach
4 to a signal like that.

5 DR. TEMPLE: But the concept here, which was,
6 obviously, some degree of compromise, you could have
7 insisted that the 1.3 be ruled out prior to approval.
8 You could have. But the committee grappled with that,
9 and I think -- the committee will have to say whether
10 this is what they were saying -- they said we're going
11 to rule out something high as a first step so that we
12 don't essentially block permanently all approval of any
13 new anti-diabetic drugs. And we'll take some
14 reassurance from that and the point estimate -- it
15 shouldn't be too bad -- and then we'll really pin it
16 down.

17 So, I mean, you could argue that there's
18 another way to do that, but that's sort of what it was.

19 DR. THOMAS: Stay tuned until tomorrow.

20 Dr. Proschan?

21 DR. PROSCHAN: Yes. I think there's a
22 packaging issue. I mean, at 1.8, people look at and

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

333

1 say, were you high when you came up with that number?
2 Nobody should be happy with 1.8. But actually, there's
3 a different way you can look at it, which is doing that
4 procedure has certain properties. And one of those
5 properties is that if the actual hazard ratio is 1.5,
6 then you have this much power, of showing that. If the
7 actual hazard ratio is this amount, you have this much
8 power.

9 So I would think that a good thing to do
10 would be not to necessarily force people to go through
11 that, do this non-inferiority type analysis, but just
12 say come up with some criteria for determining whether
13 your drug is acceptable, and it must have the following
14 properties. If the actual relative risk or hazard ratio
15 is 1.5, it must have at least 75 percent, or whatever
16 number you want to come up with, power of declaring
17 that it doesn't pass. And if the actual hazard ratio
18 is blah, blah, blah, then it must have a certain power,
19 whatever procedure you come up with. That way it
20 doesn't -- because people who look at this -- I've
21 heard people talk about this and say, "It's crazy. 1.8
22 is crazy." They're getting bogged down in what I think

1 is sort of irrelevant. The only relevant thing is
2 what are the properties of this procedure. So I think
3 it would be good to just sort of repackage things.

4 The other thing is, fortunately, the scenario
5 that Marvin brought up probably can't happen. With the
6 number of events that it would take to rule out a 1.3
7 when you're seeing a 1.17 is so great, probably, that
8 companies couldn't do that. I mean, theoretically,
9 it's a concern, but in a practical matter, it's not.

10 DR. THOMAS: Dr. Rasmussen?

11 DR. RASMUSSEN: So I'd just like to address
12 Dr. Colman. In your presentation, you showed that
13 there are different populations pre-approval and in
14 post-approval studies. And I was just wondering, for
15 the CRESCENDO study, was there any evidence of benefit
16 in that population? Are we compromising the risk-
17 benefit evaluation if we impose more risk-based
18 patients pre- approval?

19 DR. COLMAN: I'm not sure I understood your
20 question. Could you rephrase it?

21 DR. RASMUSSEN: Maybe I'm preempting some of
22 the discussions that we'll be having tomorrow, whether

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

335

1 we should require more high-risk CV patients pre-
2 approval to rule out a upper bound of the 95 percent
3 confidence interval. But by doing so, we will likely
4 be including older patients with established
5 cardiovascular risk disease. And I'm wondering whether
6 including more of those types of patients will
7 compromise the benefits side of doing the benefit-risk
8 evaluation.

9 DR. COLMAN: Yes. And it might be that if
10 the program had the resources to do this, that that
11 would just be one component of the program, and that
12 there would be other, smaller, shorter-term studies
13 where they could study lower-risk individuals, younger
14 individuals for shorter periods of time.

15 DR. RASMUSSEN: But my concern was based on
16 the fact that the SCOUT study didn't really -- I mean,
17 it looks like it wouldn't actually be able to be
18 approved if it was submitted pre-approval. And I was
19 just wondering whether it was a similar picture for the
20 CRESCENDO study, that they didn't manage to get very
21 much weight loss.

22 DR. COLMAN: They didn't report the weight

1 loss with CRESCENDO. And I know that I saw some
2 correspondence after the CRESCENDO trial was
3 terminated. Some people felt that it was justified to
4 keep the CRESCENDO trial going because if, in fact, it
5 showed a reduction in the risk for cardiovascular
6 death, MI, and stroke, some would argue that would
7 outweigh the risk for suicide.

8 DR. THOMAS: Dr. Kaul?

9 DR. KAUL: Thank you. I have two questions.
10 Slide 39. Is it your contention that the enrichment
11 strategies reflected in drug C and drug D seemed to
12 have achieved the goal of increasing the event rates?

13 DR. GUETTIER: Yes. Some of these -- the
14 details of both of these drug programs aren't given to
15 you. But the sponsors could actually either do a study
16 in a high-risk population, for example, a population
17 that has just had an acute coronary syndrome. And so
18 most of the events actually in these trials, are driven
19 by the dedicated cardiovascular outcome studies.

20 DR. KAUL: Let me offer you an alternative
21 interpretation, and correct me if I'm wrong. If you
22 look at the drug A and drug B demographics and compare

1 them with drug C, the only thing that stands out is the
2 history of atherosclerotic cardiovascular disease.
3 Even though the number of events has gone up, when you
4 look at the comparator events rate, it's not too much
5 of a difference. So the enrichment probably worked,
6 maybe negligible.

7 But now contrast drug D with drug C, and I
8 don't see much of a difference there. There are a very
9 few imbalances, but they each balance these out. And
10 yet, despite the increased number of events, similar
11 amount, the comparator event rate is almost twice, more
12 than twice. So if the enrichment strategy has worked,
13 it has worked negligibly in one and inconsistently in
14 the other.

15 DR. GUETTIER: Just a couple of caveats.
16 It's difficult to compare the two programs head to
17 head. What you're not seeing also here is some of the
18 other risk factors at baseline that were mentioned in
19 the talk, which is basically, now, in order to get into
20 some of these cardiovascular outcome trials, you need
21 to have hypertension. You need to have dyslipidemia.
22 And so, I mean, enrichment is definitely ongoing.

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

338

1 DR. KAUL: But we just learned from Dr.
2 Colman's analysis that history of risk factors for
3 cardiovascular disease does not have as much of an
4 impact as evident cardiovascular disease.

5 DR. GUETTIER: Yes. The other thing is some
6 of these patients are actually recruited based on the
7 fact that they have ASCVD, so that's usually documented
8 by --

9 DR. KAUL: Yes. It may be just a fluke here,
10 but that's something to look into in other products and
11 see if there is a consistent impact of enrichment
12 strategies, because that will have an impact on the
13 discussion tomorrow.

14 The other question that I had for you was
15 that I'm also somewhat intrigued by the term
16 "reassuring point estimate." And I'm sure there is a
17 very good reason for the FDA to be deliberately vague.
18 But is there an operational definition of "reassuring
19 point estimate?" In other words, perhaps I will extend
20 the question. Maybe that will help answer the question.

21 Is there a constant, predictable relationship
22 between the 95 percent upper bound of a confidence

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

339

1 interval and the point estimate?

2 DR. GUETTIER: I would ask Dr. Soukup to
3 answer this question because this is beyond my area of
4 expertise.

5 DR. SAHLROOT: Todd Sahlroot. There is a
6 relationship for time to event data. If you power for
7 1.8, 90 percent power, you need 122 events. And you
8 can achieve that boundary with a point estimate of
9 about 1.26 or 1.27, which would give you an upper bound
10 just within 1.8 and a p value of about .025. So the
11 point estimate with 122 events can't be higher than
12 that in order to also still achieve the 1.8.

13 DR. KAUL: So the determination of
14 reassurance is, again, predicated on what the expected
15 benefit should be? I'm coming back to not fixing the
16 boundaries, because the reassuring point estimate will
17 take care of itself if the boundaries are not fixed and
18 contingent upon what the benefit is or the magnitude of
19 benefit is.

20 DR. KONSTAM: I mean, I think we have to be
21 careful. You shouldn't have to prove a lack of safety
22 to not approve a drug. Right? I mean, if you have a

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

340

1 point estimate of 1.25 or something, and you've met the
2 upper boundary of 1.8, I don't think it's sufficient to
3 say, well, you haven't proved that there's an excess
4 mortality; therefore, we will approve the drug.

5 I'm pretty sure you don't want to say that.
6 Right? So I think the panel and I think the agency has
7 to reserve the right and the judgment to say, okay,
8 there actually is a worrisome signal here. And even
9 though -- so we've met the sufficient upper boundary of
10 1.8, so that's sufficient. That's necessary. It's not
11 sufficient. It's necessary. But I'm still left with a
12 worrisome mortality signal, and I'm not obliged to
13 approve the drug with a worrisome mortality signal.

14 DR. THOMAS: So why don't we have Dr. Parks
15 answer? And then what I think is probably best, is
16 this is excellent material for discussion tomorrow.
17 And we do have some speakers that will not be here
18 tomorrow. So if there are any additional questions,
19 I'd like to try and get to questions specific to their
20 presentations.

21 So Dr. Parks?

22 DR. PARKS: So I know that we seem to be hung

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

341

1 up on this boundary of 1.8, 1.3. Perhaps, it would
2 help us to get past that, to recognize that that's more
3 of the roadmap, so that we can advise companies, when
4 you start up your program, when you design your program
5 to provide us with evidence of not having unacceptable
6 cardiovascular risks, you have to at least meet that
7 threshold. And at the end of the day, as I keep on
8 emphasizing, we look at the entire profile.

9 I don't remember if it was Dr. Alexander or
10 Dr. Hiatt who mentioned the liraglutide program.
11 Clearly, that program -- I can speak about because I
12 was on the advisory committee. But if you remember,
13 that program there, some of the analyses, the upper
14 bound may have been 1.7. But if you looked at the
15 point estimate across all the different analyses, they
16 were all below 1.

17 So there was that consistent pattern, and
18 that's what I want to convey to the committee here, is
19 that we just don't look at one number and say they made
20 it. We look at a lot of things.

21 DR. THOMAS: Actually, I think we're going to
22 just try and get the questions in, especially for the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

342

1 speakers who aren't here. So we're going to start with
2 people who had questions from this morning, and these
3 would be for the three speakers who won't be here
4 tomorrow, which are Dr. Wing, Dr. Eckel, and Dr.
5 Knowler.

6 Just as an aside, "reassuring" could be if
7 you need an advisory committee or not -- right -- to
8 help you with the decision.

9 But Dr. Konstam, did you have a question from
10 early this morning, for one of the speakers?

11 DR. KONSTAM: I had a question for Dr. Wing,
12 if she's still here. Yes. I don't think we touched on
13 this statin imbalance very much from your data. And I
14 guess, looking at that, my first thought is that that
15 has the potential to severely confound your ultimate
16 cardiovascular endpoint. I could imagine that that
17 kind of post-randomization imbalance can easily creep
18 its way into randomized obesity drug trials.

19 When I looked at the LDL cholesterol
20 differences between the two groups, they actually were
21 pretty modest, I thought. And I wondered what you can
22 tell us or conjecture about what caused the statin

1 imbalance, and is it that there actually was a
2 favorable trend in your -- one could conjecture that
3 you actually could have a favorable effect on LDL
4 cholesterol, which resulted in a higher statin use in
5 the control group. And I'm not sure there's any
6 evidence for that. But you could imagine the use of
7 statin might, in fact, be an endpoint.

8 I just wondered if you could think about
9 that.

10 DR. WING: Right. Those are things being
11 considered. I mean, I think the -- I'll answer you in
12 terms of Look AHEAD, and I'll try to talk a little bit
13 about the implications I think for you all on other
14 drug studies.

15 In Look AHEAD, keep in mind you cannot
16 double-blind a study such as Look AHEAD. People know
17 and the doctors know whether the person has been losing
18 weight or not and whether they're in the active
19 treatment or not. So our hypothesis is that if a
20 person comes into their physician, and their LDL
21 cholesterol is high, and they know they're not in the
22 weight loss arm, that they may say, "Gee, I better

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

344

1 start you on a statin," whereas if they're in the
2 weight loss arm, they may say, "Let's wait three more
3 months and see if the weight loss is going to kick in."
4 So that's a possibility.

5 I think the implication for you all is that
6 you need to think very carefully if you're going to be
7 arguing for trials looking at these CVD risk reductions
8 or CVD effects, that who is going to be doing the lipid
9 medication adjustment, or are you going to develop -- I
10 mean, are your investigators going to do it? Are their
11 local physicians going to do it? And are there going
12 to be very set algorithms that if the person's LDL is
13 this, then they start on a statin, and if it's this,
14 they don't.

15 But those would be ways that you, in a
16 double-blind trial could deal with some of these
17 issues. We made the decision, as they say, that we
18 wanted not to regulate all their medications. We
19 wanted that to be done by their own physician.

20 DR. KONSTAM: So do you have any hint about
21 why they wound up on less statins, if you were doing
22 the lifestyle intervention?

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

345

1 DR. WING: I thought I answered that. We
2 think that they were on less statins if they were in
3 lifestyle intervention because the physician was
4 willing to wait longer and say, "Okay. Your LDL is
5 still high, but we will see."

6 DR. KONSTAM: Even though you've now
7 documented that lifestyle intervention actually raises
8 your LDL.

9 DR. WING: No. Lifestyle intervention didn't
10 raise the LDL.

11 DR. KONSTAM: I'm being a little bit
12 facetious, but it certainly didn't show that you
13 improved it.

14 DR. WING: Keep in mind that these changes
15 are going on as we're analyzing the data, so these
16 aren't out there. But I also think the point that you
17 made is very true, that these are very small
18 differences in LDL cholesterol. With 2500 in each
19 group, we can see that as a statistically significant
20 difference.

21 I think the other implication of this finding
22 that I really would pressure you to think about is two

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

346

1 things. Number one, that more and more people are
2 being treated with statins. There's better blood sugar
3 control. There's better hypertension control. So
4 you're going to have to look at what's going to happen
5 to the event rates in these studies.

6 I was very surprised that your event rates
7 that you're showing me in many of these trials looked
8 so high compared to the event rates we're seeing in
9 Look AHEAD. Now, some of that is because we did do
10 GXTs. We did select healthier patients. But I also
11 think that if you're doing trials, in the United States
12 especially, and with diabetics where there's more and
13 more emphasis on increasing the use of lipids,
14 increasing their blood pressure control, that you're
15 going to be driving down your risk factors, and you're
16 going to have more and more confounds with medication.

17 So I think these have implications to you way
18 beyond the Look AHEAD trial that I would be thinking
19 about for other CVD obesity drug trials.

20 DR. THOMAS: Can I ask one favor from the
21 speakers? In their clarification of the questions,
22 that they can stay actually to the content of their

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

347

1 talks.

2 DR. WING: I'm sorry.

3 DR. THOMAS: That's fine.

4 Dr. Rasmussen?

5 DR. RASMUSSEN: So this is actually also a
6 question for Dr. Wing. You nicely showed that there
7 was a correlation in the Look AHEAD study between
8 amount of weight loss and improvement in cardiovascular
9 risk factors. Does that also apply when you look at
10 different age categories? Did the eldest improve just
11 as much?

12 DR. WING: I don't know that data. Okay? I
13 do know that the severely obese improved just as much
14 in the risk factors with weight loss. They did not
15 however -- the severely obese started out at higher
16 levels. They had the same improvement, but still at
17 the end of the study had higher levels of risk factors.
18 I don't know that by age.

19 DR. THOMAS: Dr. Jensen?

20 DR. JENSEN: I had a question for some of the
21 information we received this morning regarding the
22 real- life use of anti-obesity drugs from the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

348

1 surveillance data and if there's any information about
2 the age groups that were prescribed these.

3 The reason I ask is my impression is we tend
4 not to prescribe anti-obesity drugs for the elderly,
5 which might be the group that we're looking to enrich
6 in order to have a better detection of a cardiovascular
7 risk signal.

8 Did you have prescription in surveillance
9 data by age group, and what proportion would be in the
10 older groups that we might be looking at for the
11 future?

12 DR. BORDERS-HEMPHILL: We did look at the
13 prescription use by age. It was slide 16, I believe.
14 And this is the proportion of patients with a
15 prescription claim for orlistat, or phentermine, or
16 sibutramine by age. And the 65-year age group for
17 orlistat was 14 percent of that total. And phentermine
18 was 5.4, and sibutramine was 8.5 percent.

19 DR. JENSEN: And phentermine makes up 90 plus
20 percent of the prescriptions, it looks like. Right?

21 DR. BORDERS-HEMPHILL: It was a higher
22 proportion of those three and of the other total. And

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

349

1 earlier in the presentation, I looked at all anti-
2 obesity medications by dispensed prescriptions. That
3 was the graph with the lines and the total. And
4 phentermine, for even amongst these three, it's the
5 predominant product being used.

6 DR. THOMAS: Dr. Goldfine?

7 DR. GOLDFINE: Dr. Wing, I'm sorry. Can you
8 come back for Look AHEAD again?

9 DR. WING: I'm glad I'm sitting near the mic.

10 DR. GOLDFINE: Thank you.

11 What I'm wondering about, I mean, there's
12 sort of a hope that if you start an anti-obesity drug,
13 that patients would lose weight and then be able to
14 sustain the weight loss even once they stopped the
15 drug. And to date, that really hasn't proven true.

16 What you actually showed was that you had
17 this intervention that was lifestyle, and that then
18 they were able to sustain not all of the weight loss,
19 but really a remarkable amount of sustained weight loss
20 over time. Yet, you made the comment that while they
21 were coming for their visits, they were not adhering in
22 any measurable way, to a relatively large degree, with

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

350

1 the continued recommendations.

2 I'd like you to expand upon that because I
3 guess I had always assumed that you had changed their
4 behavior in ways that they were then continuing over
5 time. I'm not at all surprised that the weight loss at
6 one year predicts the ability to lose weight. You've
7 found a responder population. So if they were able to
8 lose weight, then you have a responder population. But
9 do you have any idea about, scientifically or
10 clinically, what's helping them maintain that weight
11 loss? Because I think that's very important.

12 DR. WING: I pointed out this morning that we
13 did keep the intensive lifestyle intervention going the
14 entire time. And I would say that those people who
15 maintained the behavior changes the best are the ones
16 who maintained the weight loss as the best. And I
17 showed that -- I don't know the number of the slide.
18 But I showed that in those people who had lost 10
19 percent of their body weight and then kept it off, that
20 they were the ones who had kept the best use of the
21 meal replacement, the best physical activity.

22 So I don't have numbers. It would depend on

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

351

1 what variable we're looking at, but there's clearly
2 some people who stop attending as many meetings.
3 There's some who don't do as much physical activity.
4 And those are the ones who are at risk for regaining.
5 Those who continue to do those behavior changes are the
6 ones with the best long-term weight loss.

7 DR. GOLDFINE: So when you said that while
8 they were coming back in but they were certainly not
9 being adherent at the same rate, that's true sort of
10 globally, but the responders are still those that are
11 adhering?

12 DR. WING: That's a good point. Yes.

13 DR. GOLDFINE: Thank you.

14 DR. THOMAS: Dr. Capuzzi?

15 DR. CAPUZZI: I just want to make a comment.
16 This discussion today was extremely difficult and
17 tricky, and it's hard to make statements that are not
18 affected by other variables. But just in the field
19 that I'm focused in, which is lipid regulation, there's
20 a dramatic effect of -- beneficial, stabilizing effect
21 of using combination lipid-lowering therapy, not just
22 statins, but how you use it, how you direct it to the

1 metabolic problem. I mean, you put any diabetic on
2 weight loss drugs on top of that and it's very hard to
3 describe or even infer what the results of a trial will
4 be. You're affecting the artery wall. You're
5 affecting not only the lipid levels, but their
6 modification of lipoproteins charged, glycosylation,
7 everything else, by the baseline agents that they're
8 taking.

9 So I'm really impressed with the discussion,
10 but there are so many factors involved, and it's very
11 hard, I think, to come out with commandments or basic
12 statements that are not carefully identified.
13 Otherwise, you just get yourself in difficulty.

14 DR. THOMAS: Dr. Alexander?

15 DR. ALEXANDER: I've had my questions
16 answered. Thank you.

17 DR. THOMAS: Dr. Yanovski?

18 DR. YANOVSKI: I guess this question is for
19 Dr. Wing. It's very clear that, at least for most of
20 the cardiovascular and other complications that you've
21 looked at, that weight loss has a really strong
22 relationship with improvements in virtually all of

1 them. And when we come to look at drug therapy,
2 because drugs are going to be imperfect, there's going
3 to be some instances where there's not going to be
4 improvements in one or more of these that are seen with
5 equal amounts with weight loss generated by behavioral
6 therapy.

7 It's sort of a more theoretical question, but
8 how should we approach this? Should we demand --
9 should we insist that we see every bit of the
10 improvements that you can see with weight loss by non-
11 drug means, with drug therapy? How much -- what do you
12 think?

13 DR. WING: I would hope that your comparator
14 had a lifestyle intervention and that you are looking
15 for the active drug treatment to show improvements
16 relative to that. That's I think your decision whether
17 it's every single outcome measure.

18 DR. YANOVSKI: Yes. I guess what I mean to
19 say is that I think in a lot of drug trials, the weight
20 reduction, because that's what the trial is designed to
21 see, will be greater in drug than placebo. But if we
22 saw no marked improvements in many of the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

354

1 cardiovascular or other risk factors, maybe a couple,
2 but the vast majority really were not improved, even
3 though the weight loss was greater, would we be happy
4 with that? And what do you think?

5 DR. WING: I'm a little unsure how you want
6 me to answer after having the comment that I went
7 beyond my talk this morning. So I would guess that, to
8 me, you're using your lifestyle intervention as your
9 benchmark. And you would hope that it's not only the
10 weight loss that you want; it's the weight loss and the
11 CVD risk factors. So if your drug improved the weight
12 loss over lifestyle, I would also hope the drug would
13 improve most of the risk factors over lifestyle. And I
14 think that's what has been concerned about sibutramine,
15 where some of the risk factors were not improving
16 relative to the control group.

17 DR. YANOVSKI: Right. But even if they were
18 just as good as the placebo group, but not better,
19 despite greater weight loss, wouldn't we be unhappy?

20 DR. WING: Certainly would be happier.

21 DR. THOMAS: Dr. Hendricks?

22 DR. HENDRICKS: Forgive me for a practical

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

355

1 question at the end of the day. So since we've made
2 these changes in the criteria for the diabetes drugs,
3 what's actually happened to the time that it takes to
4 get them approved and the cost to the company to
5 actually accomplish these outcome trials? Does anybody
6 have any data?

7 DR. PARKS: I just want to make sure I
8 understand your question. You're asking the impact on
9 the drug development time?

10 DR. HENDRICKS: Right. Time. And obviously,
11 these are going to be more expensive to conduct, so
12 what's happened? How long does it take to get a
13 diabetes drug approved with these new criteria?

14 DR. PARKS: I don't have that information. I
15 imagine that PhRMA has been tracking that. We
16 certainly are looking into that as well. There are
17 just no illusions here. I think that when you see the
18 kind of numbers that were displayed here, where the
19 patient-year exposure is at least double, that there's
20 probably going to have to be some increase in duration
21 and probably cost as well.

22 The slide that Dr. Guettier put up there --

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

356

1 again, with an understanding it's hard to compare
2 across trials, those were also mean numbers, mean
3 percentages. But we've looked at this as well, and
4 what's really quite amazing is that you're starting to
5 see a patient population study in a diabetes program
6 that looks a lot more like the patients that you see in
7 your office. So you see more patients with renal
8 impairment.

9 I can give you an example of a program before
10 the diabetes guidance was put in place where the number
11 of patients with severe to moderate renal impairment
12 was in the single digits. And now, we're seeing -- I
13 think -- I don't know if it was on this slide, but in
14 terms of percentage, maybe 4 percent of the entire
15 study cohort. Now, we're seeing somewhere from 14 to
16 18 percent of patients with renal impairment.

17 Some of the trials before the diabetes
18 program was implemented excluded patients with
19 hypertension. So if you see diabetes patients without
20 hypertension, then that might work. But if most of
21 your patients have both diabetes and hypertension,
22 these programs probably give you a lot more information

1 about the efficacy and safety in the general
2 population.

3 DR. THOMAS: I have a question for Dr. Wing
4 and Dr. Knowler. One of the features of both the Look
5 AHEAD and DPP trials is the success in subjects being
6 retained in the trial for observation and endpoint
7 monitoring.

8 The lifestyle intervention is probably fairly
9 intensive. How is that compared to the lifestyle
10 interventions in our pharmaceutical trials? And could
11 the differences in lifestyle intervention play a factor
12 in the ability to have subjects retained at a higher
13 level?

14 DR. WING: George, you actually may be able
15 to answer that better than I can, but I think the
16 lifestyle intervention across the drug trials has
17 varied tremendously, with some of them being very, very
18 light in their intervention, but others having more
19 robust lifestyle interventions. And the weight losses
20 in those conditions sort of parallel that difference in
21 the intensity, where some of the trials have actually
22 gotten quite good weight losses in their lifestyle-

1 alone group. So I think it does vary across the
2 different drug companies' studies.

3 Whether that relates to the long-term
4 retention in those trials, I don't know. I'd have to
5 look at those different studies.

6 George, I don't know if you know.

7 DR. KNOWLER: No.

8 DR. THOMAS: Dr. Bray, if you have input, I'm
9 happy to have it.

10 DR. BRAY: Yes. The criterion that are used
11 on this side and the other side of the Atlantic in part
12 determine how intense lifestyle is. If you look at the
13 European trials -- I showed the orlistat one, but the
14 other ones from Europe are similar -- their lifestyle
15 is about 6 percent. In the Redux trial, it was 7
16 percent and the drug was another 2 percent.

17 On this side, the drug you just reviewed had
18 an effect of, what, 1 and a half percent or something
19 of this sort. And the reason in part is that we
20 require 5 percent below placebo as one criterion, so
21 you don't want a very big placebo effect. In Europe,
22 that's not a criterion, so you can have as big a

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

359

1 placebo effect as you want. But if you look at the
2 trials in general, the European lifestyles are not far
3 from what we're getting in DPP and Look AHEAD. If you
4 look at them on this side of the Atlantic, they rarely
5 are. So we could clearly do better, but you have to
6 change your criterion on which you're going to make the
7 assessments to do that.

8 DR. THOMAS: Dr. Gregg?

9 DR. GREGG: Yes. The thing I'm struggling
10 with in terms of making this leap from the policies
11 with diabetes drugs to the obesity drugs is that the
12 using population is really potentially a very different
13 age. The diabetic population is essentially half or 60,
14 65 and older. And so the fact that when you talk about
15 enriching to get there, you're actually moving it
16 closer to the target population. But with obesity, I
17 think, at least if we can believe that data from this
18 morning, it's actually the opposite situation, where
19 there's only about 10 percent of the using population
20 in that group.

21 So I think what that means for us -- and I'm
22 getting to the question -- is that this 1.3 sort of has

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Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

360

1 some face validity and is a potentially practical
2 target to use for assessing risk when you have an older
3 population, when the event rates are pretty high. But
4 the reality is that the using population of the obesity
5 drugs, the event rates are actually much lower, or even
6 I think than the lower examples there.

7 So I think what this leads us to is that
8 we're putting ourselves in the position of using the
9 older population as essentially the sentinel for
10 whether these drugs cause excess risk in the using
11 population.

12 So the question -- I don't know whether Dr.
13 Bray, Dr. Eckel, or one of the cardiologists here can
14 address -- is that to the extent that these drugs might
15 cause excess risk, can we expect that the younger
16 population will reflect that in the same way that the
17 older population would? Is that a reasonable --
18 because I think that's where we're going to find
19 ourselves tomorrow in our discussion.

20 DR. THOMAS: Dr. Temple?

21 DR. TEMPLE: I'll be interested in what Curt,
22 Mary, and others say, but I think the presumption in

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

361

1 all this is that if you show an adverse effect in a
2 selected higher-risk population, it's reasonable to
3 assume that the direction of the effect is going to be
4 similar in a lower-risk population.

5 We certainly act that way when we consider
6 drugs for treatment, whether it's lipid-lowering or
7 heart- failure drugs. And almost always -- you may
8 need a much larger study to show it, but the direction
9 is usually in the same way because it's doing something
10 that may be less common in the lower-risk population,
11 but it's still potentially there.

12 But I think that's the fundamental
13 assumption, that you can't detect it in a low-risk
14 population. They'll just never have the event. So
15 forget about that. But if you find it in a higher-risk
16 population, you are now appropriately and almost
17 certainly nervous about the fact that it's going to do
18 something in a low-risk population. Now, if it had
19 some wonderful advantage in that population, that might
20 overcome your concern, but I think that's the
21 underlying presumption. Right?

22 DR. PARKS: I don't know if I feel the same

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

362

1 way. I think one thing here is you may be studying it.
2 You may see a risk in a high-risk patient population.
3 And could it be that the horse is already out of the
4 barn?

5 I'm really not trying to direct tomorrow's
6 conversation. I think that what, Dr. Gregg, you raise
7 here is what the panel has to debate. I know you all
8 want to hear what the FDA thinks about this. But what
9 you're seeing are differences or similarities between
10 the two patient populations, and whether or not that
11 fits the paradigm is what you need to bring to the
12 table tomorrow.

13 I hear what you're saying, Bob. It is
14 concerning if you have a high-risk population, and they
15 can do the studies, and it shows harm, does that
16 automatically mean that there's going to be absolutely
17 no benefit in a low-risk population?

18 We recently discussed at an advisory
19 committee the issue of statin therapy in patients pre-
20 dialysis and on dialysis. And the question was raised,
21 well, perhaps not having seen benefit in the dialysis
22 patient population is because they've already gotten

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

363

1 too far along in their disease process and we didn't
2 intervene at an earlier stage. I don't know if that
3 would be the case here with obesity drugs.

4 DR. TEMPLE: Mary, that's always part of the
5 discussion, but it's worth noting that for in people
6 who have always worried about maybe people are too far
7 gone to benefit from drugs, talking about benefit. But
8 in heart failure, in lipid lowering, in blood pressure,
9 it's always been true, every time now, that when you go
10 to the less sick population and increase the study
11 sample size appropriately, you see the same direction
12 of effects.

13 So there may be a case where that's not going
14 to be true, but history says that's not so likely, I
15 think.

16 DR. THOMAS: We probably have time just for a
17 couple of questions. So I know there's a lot of
18 interest, but we'd like to really focus if there are
19 questions for our three speakers who are leaving today.

20 Dr. Bergman?

21 DR. BERGMAN: Maybe this is for either George
22 or Rena. So I continue to be surprised that a small

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

364

1 weight loss has so much effect. This is something that
2 I've never understood. It doesn't make sense. But it
3 implies that the individuals being studied are
4 somewhere near their set point for their body weight.
5 And so you're kind of moving them off the set point and
6 that has a lot of positive effects. But there's also
7 the danger that if you study patients, they're not at
8 their set point. So I think this kind of reflects in
9 Rudy Leibel's work on weight loss in a variety of ways.

10 So if you happen to study patients who come
11 in, and for some reason, let's say they happened to
12 have gained weight recently, or one way or another
13 they're above -- assuming there is such a set point,
14 even in obese individuals, that you could get better
15 results than you should because are you really bringing
16 them back to where they would be anyway, this could
17 change one's perception of what a given treatment would
18 do, particularly, I would say lifestyle; if you
19 interview them and somehow, because of the way you're
20 choosing them, you happen to choose people who went on
21 kind of a binge for the last three months and now
22 they're coming back to where they should be.

1 Is there any way to establish whether that's
2 true or not? Because I think it could bias weight loss
3 data. Now, this isn't directly related to what we're
4 doing tomorrow, but it may have something to do with
5 why such a small weight loss could have so much
6 positive effect.

7 Maybe, George, I'll pin this one on you. You
8 may be the best person to try. Rena, I don't mean
9 anything personal.

10 DR. BRAY: Rich, I think there may be in the
11 overfeeding studies in humans, where in almost all
12 cases, they go up and they stop whatever the experiment
13 is, they come down quickly. So that's the group of
14 people. If you've got people who have done some of
15 that, they're more likely to come down if you begin a
16 treatment with them.

17 I think your point about whatever leptin or
18 other things may be doing as you acutely lower weight
19 may be very important, and maybe that's something we're
20 going to have to change later. But I think your point
21 is quite right. If you're a little above or a little
22 below, you may well get a different response. But

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

366

1 presumably, if you randomize enough people, you're
2 going to get around that issue.

3 DR. BERGMAN: It would depend on how you did
4 the pre-approval selection, which I think is -- anyway,
5 it's worth thinking about.

6 DR. WING: The run-in period for these trials
7 is usually several months, where you're consenting the
8 person, talking to them, meeting with them. So it's
9 very unlikely that what happened in the month or two
10 right before would be having such a major impact. We
11 certainly don't select people who have recently gained
12 weight in hopes that, then, we're going to be showing
13 that they're going to lose weight.

14 I think the most interesting thing about the
15 question you're raising is you actually see a 10
16 percent weight loss having a very dramatic impact even
17 on people who start very heavy. So even in the
18 severely obese individuals, if they lose 10 percent of
19 their body weight, it will have a very large impact, as
20 it will with a much less overweight individual. And so
21 I think that's a very interesting finding.

22 I think there's some evidence that the

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

367

1 benefits of a 10 percent weight loss, even if you
2 maintain the 10 percent weight loss, are not as great
3 for certain measures over time. That certainly
4 happened in the SOS study, where people lost large
5 amounts from surgery. Blood pressure improved
6 tremendously initially, but when you looked at them 10
7 years later in the SOS study, blood pressure had not
8 improved relative to the control group.

9 So some of these benefits with weight loss,
10 even if the person is stabilized, may not last forever
11 if you go long enough.

12 DR. THOMAS: Ms. McAfee?

13 MS. MCAFEE: I have to tell you, Rena, I have
14 never gone on a diet in my life where I didn't spend a
15 few days ahead of time having good-bite-of-food
16 parties. I think it's just really common that people do
17 that. Maybe they don't do it for a couple weeks, but I
18 think, particularly among the heavier people, I suspect
19 that you're going to find that.

20 DR. WING: I'll just try to answer you one
21 more time. The randomization weight, your
22 randomization weight might have been obtained several

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

368

1 months before, when we were really doing your baseline
2 assessments. So we don't usually take the baseline
3 assessment. They know they're starting their
4 treatment, let's say, October 1st. It isn't when they
5 start the treatment October 1st. It's when they went
6 through all the baseline assessments, which might have
7 been in September. So we sort of get around that "eat
8 right before you start the program."

9 DR. BERGMAN: I don't think you're doing
10 that.

11 [Laughter.]

12 DR. THOMAS: On that note, that will be the
13 last question for today. I'd like to thank all of our
14 speakers and especially our outside speakers, Dr. Wing,
15 Dr. Eckel, Dr. Knowler, and Dr. Bray. Dr. Bray will be
16 here tomorrow if needed for additional questions. I'd
17 like to thank the FDA presenters as well for their
18 excellent presentations and the panel for their
19 questions.

20 I'd also like to remind all panel members
21 that, remember that there should be no discussion of
22 the meeting topic, during this break period of

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

369

1 adjournment of this meeting until tomorrow morning,
2 either amongst yourselves or with any member of the
3 audience.

4 We will resume tomorrow morning at 8:00 a.m.,
5 and today's meeting is adjourned. Thank you.

6 (Whereupon, at 4:57 p.m., the meeting
7 was adjourned.)

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Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012

370

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Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 1

<u> </u> \$	228:9,10,17,19,2	310:17,20 311:1	332:22 333:2,21
\$10,000 135:14	2 229:2,4	331:6	339:7,10,12
\$100 169:12 172:2	230:13,15	1.21 282:19	340:2,10 341:1
\$3,000 10:12	231:7,9,17,18	1.25 340:1	1:00 186:7
\$30,000 135:1	232:11 233:8,12	1.26 339:9	10 13:7 17:6 33:4
<u> </u> 0	238:21,22	1.27 339:9	45:3 49:6 102:1
0 180:11	239:1,3,5,9	1.3 216:19 217:5,9	103:5 114:11
0.05 224:7	240:6,12 241:22	218:17 228:16	130:11 131:1,21
227:7,14 230:16	242:4 244:16	239:15 281:13	132:11 134:11
0.5 228:9 231:2,7	254:4,9,10	307:9 308:19	149:14 150:15
285:7	275:20 276:3,18	310:17 311:4,11	155:4,6,13
0.7 151:4	281:13 290:16	313:1,19 315:18	157:14,18,20,21
0.84 274:19	294:16,22 310:2	316:21 327:2,18	158:1,8,10,11,19
0.85 232:18	317:7 319:2	330:4,8 332:7	164:22
0.97 274:18	329:13 330:6	334:6 341:1	165:13,15 172:1
025 339:10	331:18 341:16	359:22	180:12 195:2,21
05 272:11 273:13	358:18	1.31 280:21	198:18 199:20
279:11	1,000 120:3	1.34 327:14	204:15,16
08 57:1	217:7,11	1.35 276:4	205:11 206:8
<u> </u> 1	218:16,19,20	1.36 43:2	208:9 217:20
1 15:3 21:21 33:10	219:7,9,10	1.4 232:1,3 310:17	218:1 229:12
36:14 45:14 77:2	229:22 231:8	311:7,9	261:14 278:5
141:8 155:10	232:2,16,19	1.5 217:9,18,22	280:18 295:16
157:15	1.0 330:7	218:18 219:5	350:18 359:19
158:8,9,11,17	1.00 317:7	227:1,15 228:3,6	366:15,18
159:2,9 160:7	1.03 280:21	230:13,21	367:1,2,6
162:1,5 163:11	1.1 244:22 328:20	231:10	10,000 149:22
165:4,5 180:13	329:11 330:7,17	240:4,6,11,19,21	277:2 284:13
192:18 196:21	331:14	245:3 330:15	311:5
197:8 217:2,4,17	1.10 283:5	333:5,15	10:30 116:7
218:1,14 219:7	1.12 274:19 317:8	1.51 240:12,14,20	100 70:18 122:17
220:8,12	1.13 275:21	1.7 327:17,20	143:22 148:20
221:9,10,12,22	1.15 245:1 327:21	328:3,21 341:14	100,000 30:20
222:3 223:12	331:7	1.8 216:19 239:14	100-person
224:3,5,8	1.16 280:20 282:10	307:6 308:1	122:9,10 195:17
227:6,14	283:1	309:14 310:8	10903 1:16
	1.17 334:7	315:17 327:2,9	10-pound 113:11
	1.2 281:14	328:4,15 329:13	10-year 132:4,12
		330:4,7,16 331:3	133:15 135:7
			172:10

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 2

11 50:4 122:10,11 125:10 148:11 152:4 153:2 158:1 289:22 324:15 11.4 204:19 205:6,10 280:18 11.5 279:9 284:11 12 25:17 53:14 55:6 62:3 63:2 67:2 68:5,15 120:14 130:18 209:4 290:16 297:15 12,800 231:11 122 339:7,11 125 310:10 12-month 25:14 13 145:7 153:3 193:19 13.5 147:9 13.8 274:11 1300 163:9 298:17 310:22 131 228:2 14 348:17 356:15 15 41:1 114:11 148:20 165:15,16 190:11 201:7 228:1,4 232:15 261:14 273:12 276:12 279:18 284:11 150 124:19 200:17 257:1 1500 16:13 23:1 27:14 63:1,4	298:17 15-minute 116:3 270:2 15-year 104:21 16 64:5 348:13 1600 273:15 17 35:19,21 38:20 88:12,17 157:21 17.5 283:3 172 40:14 175 149:20 18 7:18 8:3,21 150:14 163:13 209:3 274:2 281:5 356:16 18,000 272:3 284:13 18,550 232:5 18.9 283:4 180 41:8 42:8 45:5 190 34:22 1970s 265:8 296:11 1972 7:9 1990s 276:12 1991 29:8 31:2 32:22 33:21 38:12 67:16 1994 259:6 1995 15:16 17:5 1996 16:10 17:15 23:18 31:5 118:14 1997 31:6,11 276:21	1998 17:21 194:19 1st 368:4,5 1-tailed 310:3 <hr/> 2 <hr/> 2 11:20 13:13 15:3 21:21 22:10 26:19 33:10 45:14,21 79:15,18,20 85:2 104:8,15,18 117:4,12 118:4,9,13 120:22 121:1 123:7 127:12 128:4 130:22 137:16 141:8,10 142:10,15 143:2 145:10,14 146:22 148:5 149:6 157:5 158:14 159:9 165:8,9,11 179:14 180:4,9 191:5 216:19 217:18,20 218:2 228:18 230:14 231:11 232:5 238:22 239:2,4,6,10,13 272:20 277:14 284:19 285:20 286:3 287:3,8 289:21 290:8,17 294:17 295:1,21 296:22 297:6,11,22 298:7,16 301:18 304:2 305:2,10,12 311:4 312:2,9,11 314:5 326:12	358:16 2,000 230:1 279:13 314:6 2.2 240:4,16 2.5 307:14 310:3 2.7 32:2 38:12 70:15,19 2.8 278:7 2.98 196:13 2/3 299:19 303:16 2:55 270:6 20 13:7 23:13 34:5 49:5 52:11,12 140:11 155:11 158:3 173:12 191:22 206:21 232:19 270:10 272:3 310:18 312:5 20,000 311:6 200 16:16 108:4 2000 17:21 28:3 271:9 2001 118:15 120:6 129:10 2002 32:1 36:15 40:12 41:22 129:14 2003 277:8 2004 18:9 2005 128:18 2006 127:5 271:18 2007 12:22 15:13 21:8 31:12 57:1 271:18 2008 11:12
--	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 3

29:15,20 34:12 36:8 57:4 272:13 274:5 294:2 296:18 301:5,7 304:18 311:16 326:5,11 2009 277:8 2010 12:4 17:19 2011 29:8,15,20 31:2 32:2,4,17 33:6,21 34:12 36:8,16 38:12,13 40:12 57:4 66:4 70:15 2012 1:10 2014 129:16 168:8 208 7:18 8:3,22 20-milligram 271:9 21 196:12,20 22 50:16 247:13 326:5 23 155:5 316:6 230,000 43:2 24 119:5 158:13 24, 135:1 25 18:19 34:7 75:19 90:10 96:2 118:19 148:6 155:3 163:11 199:20 277:11 2500 298:15 299:17 345:18 256 227:8 25th 209:7 26 52:12 290:15	26.9 277:11 27 16:21 27:18 148:7 199:16 277:10 27,000 40:15 28 1:10 2-hour 118:22 <hr/> 3 <hr/> 3 16:5,13 18:12 21:22 22:17 23:6,10 24:10 25:12 26:21 27:10 28:2,9 43:12 154:10 162:5,10,14 193:10 196:22 197:2 198:3 217:6 218:15,20 219:8 221:22 268:22 271:4 273:16 276:18,19 280:15 283:16,19,22 284:2,5,16 285:1,6 297:19 298:16 305:10,12 312:2,9,12 314:6,10 319:8 3,000 23:1 27:14 62:15 251:20 3,234 120:4 3,786 229:12 3.01 196:11,14 3.125 150:19 3.4 203:19 3.6 43:12	3.9 274:17 30 16:20 41:16 43:16 44:21 45:12 48:9 52:4 72:6 75:20 90:10 99:15 101:1,5 107:2 119:9 148:12 187:15 188:19 191:22 204:21 229:10 307:9 308:8,13,16 309:17,21 310:14,18 300 298:18 30-day 71:2,4 31 36:16 45:13 122:18 125:21 280:22 31,000 279:16 318,400 232:17 33 148:8 274:1,12 331 229:10 34 38:1 136:18 240:14 35 24:3 47:11 107:3 350 160:18 36 148:19 177:4,9 273:22 360 46:8 37 148:17 200:8 246:22 267:3 37,000 88:15 39 336:10 <hr/> 4 <hr/> 4 45:21 145:1,3	153:5,9,12,20 154:10,21 155:2,10,14,18 156:16 157:6,7,8 158:9,12,14 159:2,5,7,10,16 160:9 161:6 162:2,5,11,14 164:15 165:5 180:12 192:19 193:3,11 196:21 197:8 201:5 208:10 221:22 251:17 252:1 268:22 274:16 276:14 285:1 311:4 356:14 4.5 217:11 218:19 219:6,10 4:57 369:6 40 21:20 44:20 99:15 280:4 310:19 40s 319:8 41 43:7 42 157:19 200:8 280:2 43 38:11 199:16 284:4 44 35:19,21 38:20 45 28:6 148:7 161:16 187:5 192:11 199:10 217:10 277:10 46 155:1 47 43:7 48.8 96:2 <hr/> 5 <hr/>
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 4

5 17:6,11,12 19:1,16 24:1,10,11,13 27:19 64:21 74:3 101:22 112:1 154:12 155:1 158:2 159:20 164:22 165:11,13,14 179:17 180:8,11 194:22 197:7 198:5 199:21 204:22 230:13 231:8 232:2,16 246:22 247:1 253:20 261:12 267:15 271:10 276:19 318:7 358:20 5,000 145:9 5.4 348:18 5:00 1:11 50 23:3 32:16 44:20 47:15 50:6,14 51:2 52:5 62:22 71:11 72:6 105:5 159:20 163:17 171:22 195:19 209:4 227:2 50,000 30:15 500 16:16 298:18 51 118:20 284:5 51,200 231:9 52 23:13 5'3 52:10 53,000 273:18 54 284:3 5'4 52:10	55 235:14 272:14 277:10 56 281:21 57 188:12 58 122:19 59 148:18 596 228:5 5-HT2 26:12 <hr/> 6 <hr/> 6 120:14 130:18 198:5 200:3 358:15 60 148:17 359:13 600 148:11 611 228:16 615 309:22 63 280:2 284:3 64 42:14 273:21 65 35:17 38:17 290:19 314:14 359:14 65-year 348:16 66 45:7 <hr/> 7 <hr/> 7 120:8 125:2 158:1 161:15 194:14 211:12 279:13 358:15 7.2 40:17 7.8 122:17 70 205:1 328:16 71 33:6 712 7:19 8:10	72 32:22 64:22 65:6 73 45:8 74 154:20 74,200 232:3 75 148:7 235:14 333:15 75th 209:3 76 34:7 79 42:15 276:4 79,600 232:20 <hr/> 8 <hr/> 8 64:5 95:22 153:8 194:15 197:7 248:16 8.5 154:8 348:18 8.6 209:4 8:00 1:11 369:4 80 23:2 43:4 87:9 127:12 167:21 263:10 275:21 279:9 307:5,20 308:7 81 284:5 87 193:20 88 228:18 887 157:13 <hr/> 9 <hr/> 9 65:5 68:5 154:7 161:4 198:3 331:14 90 40:20 45:1,13 48:11,14 108:3 131:9 150:13 172:1 175:2	195:22 227:6,14 228:9 230:15 263:8 273:11 309:21 339:7 348:19 90s 67:16 71:10 90th 209:1 91 35:1 45:13 94 153:12 175:1 95 23:3 153:18 172:16,18,21 173:2 221:8,10,19 222:4 235:4 240:15 241:5 274:19 275:20 280:20 307:22 308:18 329:12 330:15 335:2 338:22 96 153:13 97 17:18 153:13 <hr/> A <hr/> a.m 116:7 369:4 A1 148:11 160:7,8,10 161:20 A1c 19:11 54:20 160:4 161:14 165:6,12,14,17 179:22 180:6 200:3,5 271:13 293:15 295:3 297:4,16 304:19 abandoned 265:8 abbreviate 120:2 abdominal 78:17 84:19 101:3
---	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 5

272:14 277:11 abdominally 78:10 Abe 11:10 ability 198:21 253:18 254:19 350:6 357:12 able 40:6 47:6 109:21 127:4 161:8 176:2 183:11 185:3 240:18 245:15 309:20 318:19 321:21 335:17 349:13,18 350:7 357:14 abnormal 286:22 abnormalities 85:6 92:20 106:21 289:4 abnormality 81:16 83:15 289:2 Abraham 2:9 4:4 95:16 111:14 absence 90:6 122:16 317:3 absolute 132:1 140:10 215:8 216:8,13 217:6,10 218:5 225:6 242:8,9,14,16 243:21 244:9 287:6 absolutely 166:7 245:5 362:16 abuse 26:14 Academy 58:14 accept 250:16	258:15 321:10 322:1 acceptable 302:14 333:13 accepted 191:16 234:18 accepting 321:21 access 134:21 accommodate 100:2 accompanied 57:19 accomplish 355:5 ACCORD 15:6 104:4 295:13 according 29:11 44:18 88:13 117:14 124:4 125:6 127:7 132:10 135:6,10 153:4 156:4 259:3 accordingly 116:1 account 31:1 216:17,22 224:10 238:5 244:6 281:21 290:6 291:1 accounted 32:16 33:10 38:15 accounts 291:16 accrued 275:8 280:13 accumulate 52:1 274:14 accumulation 52:6 accurate 100:17	accurately 108:21 178:20,21 achieve 74:3 148:8 161:21 195:22 206:10 248:12 321:22 322:15,22 339:8,12 achieved 27:20 105:8 154:3 155:7 161:18 196:8 210:7 336:12 achievement 23:10 achieving 74:2 120:8 124:19 151:2 154:7 161:13 162:12 164:13 168:17 acid 82:11 191:18 acids 80:14 81:11 acknowledge 243:2 321:13 acknowledged 10:10 acknowledging 315:19 acquiring 300:12 across 35:16 156:17 158:6 164:7 167:5 202:15 282:1 287:20 311:18 314:2 315:9 317:11 329:13 341:15 356:2 357:16 358:1 act 6:16 7:9,19 8:11 263:17	361:5 acting 9:21 285:16 action 26:2 76:22 77:1 78:21 79:12 87:3 126:4 370:9,13 actions 77:5 126:1 activations 91:2 active 22:12 23:1 24:2 27:14 62:16 100:9 102:10,12 111:16 113:20 114:19 181:9 195:7,10 214:12 215:11,15 217:16 220:4,10,14 222:15,18,21 224:16 225:8 227:5 235:17 298:4 303:2 306:5 319:16 320:1,2,19 321:11 322:17 323:17 343:18 353:15 active-controlled 319:22 actively 58:22 111:21 314:12 actively-treated 214:15 215:2 activities 124:10 134:6 activity 30:10 41:8 42:2,8,14 119:17 120:11 124:19 146:20 149:11,19 157:6 158:21 159:8
---	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 6

172:17 178:1,14,18 350:21 351:3 actual 47:18 70:10 100:13 196:4 197:3,13,18 212:18 218:17 219:7 225:9 247:22 248:9 249:10 251:6 333:5,7,14,17 actually 48:2 49:5 57:16 63:15 64:8,11 68:16 71:4 72:17 73:6 89:21 98:1 99:7 113:6 115:10,12 122:14 125:11 126:10 128:5,6 131:16 132:20 133:17,22 134:14 135:7,9 138:2,4 139:20 142:14 144:18 145:22 146:7 148:16 149:17 150:21 154:6 155:19,22 156:8,14 157:6 162:17 163:3 166:1 169:1,3,4 174:8 182:17 185:2 187:12 194:6 198:6 204:22 205:9 206:14 211:6 246:1 249:7 251:15 252:1 260:10 264:9 266:17 267:17,20 268:11 269:22 275:5 278:9	281:16 312:11 317:5 318:16 322:4 328:4,20 329:16 333:2 335:17 336:15,18 338:6 340:8 341:21 342:20 343:1,3 345:7 346:22 347:5 349:16 355:3,5 357:14,21 359:15,18 360:5 366:15 acute 83:20 336:17 acutely 287:22 365:18 Ad 121:7 ADA 161:14,21 162:12 adaptations 87:18 adaptive 245:17 264:12 add 107:20 131:8 134:17 135:5 182:17,18 183:6 187:8 197:22 214:7 221:17 253:15 added 23:19 82:6 147:20 152:22 174:19 187:20 254:17 298:2 adding 176:11 182:16 253:13,17 321:1 addition 27:2 77:22 80:4 82:21 83:18 85:5 86:6 93:18 119:18	191:1 214:20 241:3 272:21 300:15 324:7 additional 16:18 110:18 115:18 184:15 186:5 194:10 213:12 253:3,13,17,21 277:15 290:11 293:1 298:9 301:17 308:12,21 309:4,8 311:12 313:17 321:5 340:18 368:16 Additionally 236:4 add-on 306:4 address 24:20 142:21 238:9 246:16 334:11 360:14 addressed 26:6,16 179:10,18 234:12 adds 195:12 adequate 195:18 297:12 309:6 317:21 adequately 22:21 210:16 315:12 adhere 14:18 149:18 adhered 247:6,8 adherence 66:14 157:3 158:6,8 159:3 160:2 167:7 171:19,22 181:4 208:1,8,9	247:3 adherent 208:3,4,5,6 351:9 adhering 172:20 181:9 349:21 351:11 adiponectin 77:4,6 80:22 81:1 adipose 76:15,19,21 77:11,15,19 78:12,15,21 80:2,13,16 82:9 91:4 adiposity 22:5 84:15 100:13,17,20,21 101:3 209:16 288:16 adjourned 369:5,7 adjournment 369:1 adjudicate 299:4 305:9 adjudicated 313:11 315:10 adjudication 300:10,14,19 305:16 adjust 105:7 151:20 164:4 adjusted 30:22 135:13 150:7,9 151:20 235:1 307:22 308:18 adjusting 166:18 adjustment 235:4
--	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 7

<p>344:9</p> <p>adjustments 150:5 235:2</p> <p>administered 38:6</p> <p>Administration 1:4 7:6 199:7</p> <p>admit 183:9</p> <p>admitted 183:14</p> <p>admitting 173:3</p> <p>adolescence 88:19 89:1,9</p> <p>adolescents 88:13 140:19</p> <p>adult 70:18 88:21 89:3 117:14</p> <p>adulthood 88:14 132:18</p> <p>adults 88:12,18 89:10 118:1,19 138:22 143:3</p> <p>advance 212:4 238:3 295:19</p> <p>advanced 273:2</p> <p>advantage 245:18 361:19</p> <p>adverse 20:21 23:5 201:12,19 213:6 254:18 271:15 272:5 273:15 274:8 285:11 288:19 289:5 292:4 300:4,12 305:9,14 324:21 325:4 361:1</p> <p>adversely 27:8</p> <p>advice 119:17 120:20 123:13</p>	<p>129:10 133:22</p> <p>advisable 244:21</p> <p>advise 10:22 341:3</p> <p>advisor 10:11</p> <p>advisories 31:10</p> <p>advisory 1:8 2:10,12 6:15,17 7:7,8 11:13 15:18 18:9 271:18 286:10 294:2 296:18 301:5,7 304:16 311:8 317:15 326:5 341:12 342:7 362:18</p> <p>advocate 305:5</p> <p>affect 27:8 294:8</p> <p>affected 64:12 105:13 155:16 253:14 287:11,12 288:12 351:18</p> <p>affecting 352:4,5</p> <p>affects 67:13,19 68:19 290:15</p> <p>afford 8:14</p> <p>afforded 302:15 308:5</p> <p>African 123:9</p> <p>afternoon 106:4,12 186:17 211:10 262:7 285:15,18 289:17 306:21</p> <p>against 26:22 156:12 217:15 271:19 298:3 305:5</p>	<p>age 28:6 29:14 35:15 43:6 46:14,17 48:18 64:5,9,16 68:14 101:4 118:20 132:10,12 140:14 141:21 148:18 157:7 167:5 272:14 273:2,21 277:9 280:2 347:10,18 348:2,9,13,16 359:13</p> <p>aged 35:17,19,21 38:17,20 148:7</p> <p>agencies 7:13</p> <p>agency 10:5 203:5,7 265:2 271:18 340:6</p> <p>agency's 8:7 62:12</p> <p>agenda 9:4,9 10:17 12:15,17 14:17 87:16 116:20</p> <p>agent 31:22 32:3 33:13 34:4,6 35:9 296:21 297:9,21 298:1,14 306:9</p> <p>agents 39:1 55:16 70:4 206:11 302:22 352:7</p> <p>ages 132:9,11 141:11,14,16</p> <p>aggregate 147:7</p> <p>aggressive 295:14,20</p> <p>aging 176:15</p> <p>ago 14:16 52:2</p>	<p>53:5,6 80:2 117:10 130:12 132:8 139:8 143:22 187:5,13 267:3</p> <p>agonist 271:7</p> <p>agonists 26:12</p> <p>agreement 319:7</p> <p>AHA 87:4</p> <p>ahead 13:14 63:10 144:16,20,22 145:5 146:14,16 147:21 148:4 149:2 150:4,7,13 151:15 152:1,3 153:7,18 155:17 156:2 160:15 162:18 164:19 166:7 167:17 168:4 169:9,11 170:13,20 173:17 185:19 192:8 193:13,18 200:2 204:7 208:21 209:8 255:15 263:7 343:12,15,16 346:9,18 347:7 349:8 357:5 359:3 367:15</p> <p>AHI 194:4</p> <p>aim 288:19</p> <p>aimed 120:8 306:22 309:5</p> <p>aims 313:4</p> <p>airways 84:17</p> <p>akin 282:12</p> <p>al 92:4</p> <p>alcohol 91:18</p>
--	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 8

Alexander 5:16 101:10,11,18 253:4,5 254:16 255:1 257:13 341:9 352:14,15	136:3,16 187:17 194:14 206:5 207:18,19 252:2 362:3,22	166:4 200:9 214:4 218:12,14 219:2,5 221:18 236:17 299:7 316:22 333:7 337:11 347:8 349:19	299:14 300:11 301:21 306:4 308:16 312:9 315:11 316:6 329:6 333:11 338:2
algorithm 40:5	alteration 151:12		analyze 69:16 256:5
algorithms 324:6 344:12	alterations 92:5 93:3	amounts 111:20 353:5 367:5	analyzed 39:12 153:8 170:7 234:12 241:14 283:8,9
aligns 20:17	alternate 213:10 216:14 218:6	amputation 291:3	analyzing 345:15
alive 153:14	alternative 220:11 221:3 336:20	Amylin 10:11	AnaMar 107:19
all-cause 93:15 147:14 182:18	Alternatively 228:4	analyses 23:7 24:12 25:7 29:16 30:1,4 37:20 38:4 55:15 165:4 167:15 185:22 224:13 246:16,21 247:9 255:13 257:19 281:22 299:1,6 341:13,15	ancillary 185:18
allele 127:10	altogether 127:18 138:16 176:14		and/or 10:9 27:21 36:10 106:6 310:20
allergies 206:2	am 1:11 5:7 69:21 117:5 138:17 154:14 218:16 264:17 370:8,10	analysis 25:2,5 27:22 29:3,9 32:10 37:12 40:1 41:15 42:6,17,20 44:8,15 45:16 56:10 57:11 62:6 74:9 111:3,5 125:18 202:7 211:15 213:19 215:22 234:14,20 235:6 236:18,21 237:6,7,9,11,13, 14,19 238:1,3,7,8,10 241:11,16 242:17,18,22 245:17 246:2 247:5 252:16 255:5 260:21,22 275:7 282:13,15	anecdotal 114:8
Allergy 4:2 5:8	amazing 76:9 171:20 356:4		Angeles 3:5 5:3
Allison 4:16	ameliorating 294:14		angina 147:9,16 152:20 153:2 174:20 176:12 181:15,19 182:12,14,16,20 183:7,11 184:5,16 213:13 313:10
allotted 14:19	America 53:9		angioplasty 147:18 183:18
allow 10:8 23:6 200:12 227:15 244:16 262:16 305:12,20 309:1	American 53:7 86:22 117:9 123:8 141:9 142:18 202:8		angiotensin 91:2
allowed 6:12 41:16 112:6	Americans 123:9		angiotensinogen 77:2 91:3
allowing 171:6	among 40:8 53:8 123:14,21 125:3 131:15 163:21 235:15 367:18		animate 247:18
alluded 89:20 182:10 206:5 219:11	amongst 39:12 116:6 186:13 270:5 349:4 369:2		annual 32:11 121:13,16 122:7 169:11,12,19 218:8,22 231:6,7,22
alone 180:20 194:17 210:4 248:3 277:19 281:11,14,17 358:1	amount 78:3 114:5		
alpha 224:3,6,11 234:22 235:2 273:13 279:11 310:3			
already 2:5 10:17 90:20 119:18			

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 9

232:2,14,19 242:11,12 273:16 279:14 284:21 285:5 319:2 annually 30:21 34:12 119:13 answer 66:13 79:7 109:21 115:22 170:12 171:10 172:14 175:8 179:1 200:19 211:4 243:1 256:17 258:8,11 264:6 266:1 329:9,17 338:20 339:3 340:15 343:11 354:6 357:15 367:20 answered 115:2 326:4 345:1 352:16 answering 262:10 answers 138:13 antagonist 271:7 anti 34:3 36:14 39:14 48:10 57:4 66:7 70:15 103:11 349:1 antiarrhythmic 36:6,22 37:15 39:5 anticipate 233:8 234:11 242:1 246:13 248:4 anticipated 62:22 98:14 212:18 216:12 229:18 230:6 231:9,12 232:4,6,8,12,14,	20 233:6 241:21 anti-diabetic 11:17 14:13 36:6 56:1 200:9 296:9 302:21 303:15 313:18 326:7 332:13 antihypertensive 36:5,22 37:15 39:5 anti-inflammatory 80:22 anti-obesity 13:4 29:3,7,10,13,18 30:18 31:3,7,15,22 32:3,7,12,21 33:13 34:1,6,10,15 35:7,9 36:15 37:22 38:10,13,16,21 39:1 40:2 42:4 43:4,7,11,22 44:2,13,19,20 45:4,8,11,20 46:7,9,15 47:1 48:7,13,16 51:19 55:16 56:4,11 65:17 70:14,19 188:2 202:12 210:15 347:22 348:4 349:12 antiplatelet 36:7 37:3,16 39:10 antipsychotic 49:10 antipsychotics 49:12	anxious 6:21 anxiously 133:8 anybody 258:17 263:13 355:5 anymore 140:9 anyone 318:19 anything 101:15 107:21 112:2,7 115:8 133:9 164:6,16 168:18 175:16 193:5 196:17 245:22 253:2 276:2 365:9 anyway 97:15 250:11 364:16 366:4 anyways 69:13 apart 103:18 apnea 21:13 60:10 84:13 86:5 189:13 193:17,20,21 194:4,5,9 Apo 81:19,21 82:13 83:6 appear 39:13 84:15 92:21 207:13 290:1 appeared 207:14 appears 104:17 109:22 131:1 312:21 appetite 114:12 applicable 21:6 286:1 application 315:5 328:2	applications 12:5 72:2 235:13 285:3 313:14 applied 25:5 269:22 307:17 applies 326:8 apply 69:13 109:19 211:16 219:19 302:6 318:21 347:9 applying 240:13 279:15 appreciate 315:7 appreciated 86:9 99:10 approach 58:12 59:3 70:2 72:7 94:12 96:21 124:17 226:4 238:15,16,20 239:3,7,12,18 241:3 243:20 244:3 246:4 309:1,5 331:20,22 332:3 353:8 approaches 58:3,18 59:5 94:7 143:20 209:11 263:2 appropriate 16:6,21 71:20 113:18 144:16 155:22 176:8 235:5 259:20 303:1 320:9 325:19 appropriately 234:22 307:22 308:18 361:16
---	--	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 10

363:11	325:15 336:14	articles 128:18	26:11 60:5 72:20
approval 9:6	342:1 345:16	artifact 235:21	73:6 171:1
15:19 16:1 21:7	argue 180:17,22	artificially 105:22	192:21 262:15
60:19 198:15	194:15 251:5	ascertain 182:13	296:16
239:10 264:13	257:11 279:3,5	210:16	301:3,11,20,22
271:19 308:6	317:12 332:17	ascertained 184:7	302:2,5,6,9,18
309:9 332:7,12	336:6	ascertainment	313:3 315:6,16
334:18 335:2	arguing 247:13	181:21	326:7 368:3
approve 328:16,22	344:7	ASCVD 338:7	assessments 102:9
331:8 332:1	argument 251:12	aside 104:13 342:6	121:13 309:7
339:22 340:4,13	316:21	aspect 256:21	359:7 368:2,6
approved 17:16	arise 26:6	322:2	assigned 129:21
24:8 49:22 136:6	arises 222:9	aspects 89:12	assist 255:20
198:16 199:6,16	Arizona 138:19	95:11 146:16	assistant 3:20
202:18 206:12	arm 151:7	286:14 325:22	assistants 33:9
207:15,17	154:13,15	330:19	66:6
208:12 239:20	160:18 163:9	assess 12:13 16:15	associate 3:6,10
271:17 276:20	164:1 216:10,22	22:21 25:8 29:16	4:16 5:17 81:14
296:14 335:18	222:15 263:11	36:3 40:5 84:8	82:9 85:3,13
355:4,13	323:7 324:9	99:17 104:2	93:1
approximate	343:22 344:2	110:10 111:15	associated 19:17
24:14 314:1	armed 88:16	112:2 114:11	20:4 39:1
approximately	arms 147:3	115:1 196:3	46:2,12 48:17
24:3 27:13 32:16	162:5,6 169:21	221:7 223:21	60:3 61:7 76:17
38:12 62:22 63:1	321:8	228:7 239:17	78:13,18 96:18
135:14 155:11	array 288:11	301:18	102:3 108:17
159:9 279:16	arrest 204:18	assessed 59:18	109:7,10 113:8
309:22 310:10	277:5,6	99:7 119:11,13	127:11 144:5
approximating	arrhythmia 36:11	213:3 214:19	146:7 159:4
200:13	37:10 39:8	238:18 239:5	188:1 189:4
arbitrariness	arrhythmias 86:18	assessing 25:22	191:6 206:1
183:16	89:19 93:2 95:10	108:19 146:12	211:14,19 213:2
arbitrary 138:1	106:18 253:11	194:4 216:2	214:10,14
area 77:14,16 84:1	arterial 81:6 97:11	220:18	216:21 220:3,5,7
86:15 100:7,9	100:4,5	222:11,12 233:2	253:10
116:10 134:20	artery 108:11	239:12 255:15	261:11,14
339:3	183:17 272:22	360:2	286:19 287:1,19
arena 114:21	273:1 352:4	assessment 9:5	288:20
aren't 262:5		11:14 12:1 25:4	291:12,19
265:16 322:16			293:18 295:5
			307:4,8

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 11

association 33:14 47:3 48:19 59:15 68:21 87:1 215:6 216:3,15 218:6 219:20 257:10,17 assume 20:10 41:9 48:1 61:16 227:3 228:10,16 231:6,22 288:9 325:12 361:3 assumed 151:2 227:10 228:19 230:20 231:16 232:9 233:18 273:16 279:13 303:14 350:3 assumes 69:22 292:11 293:4,17 294:4 assuming 225:17 240:6 279:21 311:4 327:4 364:13 assumption 65:3 150:17 225:15 292:15 310:1 327:8 361:13 assumptions 292:19 310:9 311:2 assurance 309:4 assure 104:7,11 112:21 214:22 asterisk 327:2 asymptomatic 273:1 atherosclerotic 288:8 314:18	337:2 athrogenic 81:19 82:1 108:1 Atkins 102:19 Atlanta 3:12 4:15 Atlantic 358:11 359:4 ATP-4 104:7 atrial 92:19 94:4 253:15 at-risk 248:22 attained 124:12 131:20 attempt 177:5 attempted 270:15 attend 79:6 attendance 159:7 attendant 200:16 attended 150:2 157:4,5 158:13,15 attendees 11:7 116:18 186:20 attending 169:10,18 351:2 attention 13:22 14:4 28:13 120:10 211:3 attorney 370:11 attractive 328:21 attribute 168:18 attributed 288:1 attributes 103:14 attrition 61:14 73:2,7	ATVB 82:9 audience 10:8 116:6 176:21 186:14 270:6 369:3 Audio 370:3,19 Audit 33:12 augment 210:1 289:13 authorities 274:5 authority 7:8 authorized 8:4,11 automatically 362:16 autonomic 86:17 89:19 availability 309:19 available 37:20 90:14 199:4,5 202:5 233:16 271:21 289:15,18 290:2 309:8 Avenue 1:16 average 43:6,11 44:3,6,11 46:14,17,19 110:5 120:17 121:2 122:11 125:1,3,4 126:8 132:21 133:2 140:11,16 148:18 158:13 196:1,21 201:6 203:19 276:19 278:7 314:7 averages 209:3 avoid 219:16	278:18 303:5 avoiding 279:5 awaiting 133:8 aware 6:20 42:20 92:4 131:5 262:20 281:6 away 51:18 61:16 100:18 162:14 171:2 254:10 267:21 axes 122:8 axis 117:12 227:16,19 229:2 <hr/> <p style="text-align: center;">B</p> <hr/> background 14:12 15:16 19:3 21:4 24:17 216:17 217:17,20,22 222:17 244:11 285:21 286:4,6,7 298:2 301:7 321:20 322:21 324:14 bad 201:17 203:8,17 208:19 265:9 291:19 332:15 balance 263:10 309:6 337:9 balancing 57:22 ballroom 186:9 bang 197:6 bar 18:21 165:9 198:15,16 238:18 248:2,5 bariatric 53:8 93:15,21 94:7,11 96:21 97:6
--	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 12

101:16 112:17 255:11 barn 362:4 bars 31:4 42:4 134:18 196:19 247:16,20 base 195:18 based 9:9 33:20 41:2,3 58:16 61:3 66:9,10 73:11 113:18 122:15 152:17 171:3 214:1,2,18 215:4 222:20 224:15 237:12,13,14 239:8,10,16,20 243:18 271:21 274:17 291:21 293:13 310:1 315:6 320:13 322:6 323:1 329:3 335:15 338:6 baseline 18:20 23:8 24:1 57:22 58:21 59:5 88:16 130:21 132:22 148:15 154:19 155:12,14 159:5 160:8,10,17 163:15,22 180:2 208:11 210:11 273:4 277:17 278:14,15 297:16 299:13,22 337:18 352:7 368:1,2,6 basic 140:15 286:4 331:19 352:11	basically 52:21 81:18 128:19 164:6 165:10,12 181:4 276:3 325:11 329:5 337:19 basing 158:8 basis 189:8 202:7 207:5 219:15 245:14 B-containing 81:19 Bearing 34:4 beat 327:18 beats 276:19 became 68:9 140:18 become 66:22 131:14 137:4 142:12 250:1 becomes 75:19 142:11 beforehand 254:21 begged 104:10 begging 104:1 begin 30:18 192:1,12 199:1 281:5 286:15 325:1,8 365:15 beginning 50:22 128:8 146:15 149:3 150:12 155:9 161:12,15 163:10 197:19 208:7 271:8 begins 51:22 52:1 117:21	begs 318:14 behalf 9:21 behaves 81:13 behavior 52:20 350:4,15 351:5 behavioral 52:19 67:7 120:9,13,20 149:12 353:5 behaviors 20:18 behest 271:22 behind 14:14 58:5 189:3 belief 271:20 believe 50:10,12 76:1 84:3 131:4 139:1 155:21 243:5 278:8 348:13 359:17 believed 225:15 believes 263:13 belongings 186:8 benchmark 23:17,19 27:19 354:9 beneficial 17:8 54:18 94:15 104:3 210:3 271:13 296:6 351:20 benefit 12:9 17:2 26:1 59:16 60:12,17 61:14 73:9 97:3,13,16 103:3 104:14 127:18 128:6 160:6 162:21 187:21 189:17 191:7 193:11	245:18 258:16 261:10 262:14 268:11 293:18 294:9,14 295:10 297:2 302:15 308:4,20 309:11 312:19 318:2 321:5 328:11,12 334:15,17 339:15,18,19 362:17,21 363:7 benefit-risk 261:8,15 330:21 335:7 benefits 17:3 21:1 93:5 128:12 145:16 162:13 167:4 189:14 190:6 191:9 192:6 193:7 205:13 210:7 271:21 294:12 317:22 335:7 367:1,9 benefitted 97:2 benzphetamine 31:17 Bergman 5:1 69:18,19 78:22 99:2,3,9 100:10,16 185:9,10 266:2,3 363:20,21 366:3 368:9 Berkeley 107:20 best 12:13 54:9 63:19 110:17 111:15 124:16 160:1 174:3 180:21 183:6 184:7 256:21
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 13

263:9 322:10 323:9 340:15 350:15,16,20,21 351:6 365:8 beta 79:9,12,13 266:10,16 better 58:19 109:21 144:4 151:1 154:6 157:3,10 160:10 161:19 169:4 180:19 181:6 198:7 200:11 210:12 214:15 220:4 249:12 263:14 268:5 270:18 276:7 278:19 323:16,22 324:1 343:22 346:2,3 348:6 354:18 357:15 359:5 364:14 between-group 295:11 beyond 23:10 45:5 46:7 60:13,17 96:13 137:11,17 205:3 234:10 268:17 274:22 339:3 346:18 354:7 bias 181:22 182:13 254:1,12 365:2 biased 57:15 biggest 15:22 159:15 189:19 Bill 5:4 13:12 116:15 207:11,16 255:22 256:2,14	266:4 binge 364:21 biologics 9:6 303:19 biology 82:20 biomarker 60:1,2 61:2 294:5 biomarkers 19:10 54:18 59:19 60:6 61:8 111:15,21 112:19,21 113:9 Biomedical 211:2 Biometric 211:12 Biostatistics 211:13 birth 40:19 140:8,17 bit 59:10 85:15 88:5 106:15 122:6 130:15 131:19 134:18 135:11 139:4 158:21 172:3 180:16 240:12 260:16 266:4 274:14,21 275:19 309:13 324:18 328:14 343:12 345:11 353:9 biventricular 95:9 black 222:2 237:1 304:4,8 Blackberries 2:4 bladder 189:10 blah 333:18 bleak 252:2 blind 119:20	226:12 240:8,11 245:21 259:8,14,17 260:1 278:5 297:20 blinded 119:21 151:5 183:5 305:7 313:11 314:10 blindly 315:10 blindness 291:4 block 84:18 332:12 blood 12:6 17:8 19:10 54:20 59:19 61:1 87:12 91:6 93:6 97:4 103:7,16 106:6,11 137:22 145:19 148:10 161:22 162:3 165:18,19,20,21 166:1,15 167:11 179:21 184:11,17 191:19 202:19 209:19 256:12 258:6 271:14 276:17 278:8 279:3 287:2 288:1,2 292:3 293:19 294:11,13 324:17 325:18 346:2,14 363:8 367:5,7 blue 31:4 42:4 44:7 124:1 140:4 154:1 160:6 203:22 204:12 237:2 248:6	299:12 306:18 BMI 16:20 18:3,18,20 21:8,19 23:8 27:18 28:10 34:5,7 51:19 52:4,12 75:16,18 88:13,19,21 89:1,3,10 90:9 96:1 100:12,13,19 117:20 119:7 148:6,19 156:5 188:15,17,19 189:19 190:5 199:20 274:1 277:10,11 BMI s 18:19 22:4 101:1,4 107:2 board 122:1 129:11 Bob 6:3 13:10 97:18 99:3 260:5 362:13 body 17:7 20:12 22:5,8 24:2 25:5,10,16 26:7,10 27:6 29:11 33:14,22 75:12 77:8,10 78:5,9 84:19 87:7 90:17 101:5,6,8 102:11 117:14,18 118:2 119:5,8 121:1 143:14,17 149:15 155:1 156:10 165:13 199:14,21 201:7 247:1 286:19 350:19 364:4
--	--	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 14

366:19 bogged 333:22 bold 304:8 bolded 304:4,5 borderline 84:19 Borders 49:17 Borders-Hemphill 28:14,17,22 29:2 55:6,14 56:4,9 57:2 64:4,13 65:9,14,17,22 67:11 68:8 348:12,21 born 143:12 Boston 3:9 4:19 bother 138:4 bothering 276:8 bottom 165:7,20 198:1 202:13 208:2 209:6 327:3 331:5 bound 221:8,10,19 222:3 234:22 240:15 241:5 245:2,7 307:21 308:17 316:19 329:12,13 330:16,18,20 335:2 338:22 339:9 341:14 boundaries 261:6 326:16 339:16,17 boundary 327:13,20 328:20 329:3 339:8 340:2,9 341:1	brain 77:8 Brancati 152:13 Bray 13:15 116:22 186:17,22 187:1 207:19 211:5 243:8 246:20 247:18 248:20 249:5,20 250:1,15 255:2,19 258:3 263:5 264:18 267:2,9,12,14 268:1,8 278:3 358:8,10 360:13 365:10 368:15 break 96:2 116:3,5 142:19 186:1,6,10 270:3,5 368:22 breakdown 64:17 breaks 7:3 69:10 briefly 11:11 12:19 90:20 273:20 277:9 311:17 Brigham 4:11 bring 16:1 17:7 94:17 173:13 362:11 bringing 75:1 79:16 329:20 364:15 brisk 124:20 149:20 Brittain 4:1 54:10,11 59:9 168:13,14 245:9,10 246:3 broad 22:4	75:6,21 94:18 96:1 189:7 287:18 288:11 broaden 152:19 181:15 broader 152:15 broadly 217:12 324:20 brought 50:11 51:5 59:9 182:9 334:5 bubble 46:3,4,6 bubbles 46:5 buck 197:6 building 84:18 bulk 298:20 buoyant 83:11 bupropion 202:6 burden 183:21 296:10 bypass 183:17 199:19 <hr/> C <hr/> CABG 147:18 calamities 201:14 calculate 216:14,21 223:9,11 230:6 266:17 calculated 41:12 217:1 229:20 calculation 223:16 227:11 233:15,21 calculations 223:3 225:21 226:14	229:15 230:10,14 233:12 234:11 242:5 calendar 25:12 46:20 47:4 104:10 California 5:20 187:7 California-San 4:21 caloric 181:3 calorie 120:10 149:16 calories 124:13 175:15 181:6,7,8 257:2 Campus 1:12 cancer 75:13 85:8 182:18 189:10 191:2,8 cannabinoid-1 271:6 Canner 247:5 cap 245:2 capillary 93:8 captopril 40:7 47:2 capture 22:11 181:17 299:4 300:9 305:16 313:7 captured 30:14 38:7 292:13 293:19 294:5 295:2 315:8 captures 292:20
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 15

capturing 182:2,5	88:18,22	281:10,11	193:5 207:14
Capuzzi 28:18,20	89:2,7,10,13	283:13,21	222:17 250:17
107:4,5 108:6	91:10,17,20	284:15,20	303:10 321:20
109:2 351:14,15	93:18,20,22	285:19 287:17	322:4,6,22
cardiac 49:13 88:6	94:14,19,21 95:1	288:8	323:14 339:17
89:16,17,19,22	96:15,22 99:16	289:9,11,13	careful 151:1
93:7 95:10	101:13 102:4	291:11,14,16,18,	252:11 268:2
106:14,18,19	104:16	20 292:22	304:16 339:21
107:1 170:21	105:1,3,5,6	295:10,22	carefully 86:22
204:18 253:18	107:12	296:2,4,6,10	104:7 152:11
254:17 267:21	128:14,20	297:1 298:11	163:5,7 177:17
273:15	129:3,4,7 135:9	299:2,5,14	182:8 184:3,20
277:5,6,13	143:7 145:3,8	300:3,4,6,11	344:6 352:12
285:11	146:21 147:8,22	301:2,3,10,18,22	caring 176:1
cardinal 98:4	150:18 167:16	302:21	Carolina 3:21,22
cardiologist 3:4	183:1 188:3	303:7,10,16,18,2	carotid 147:18
4:21 5:17 86:21	189:9,16 190:17	1 304:1,7,22	carried 25:6
cardiologists 92:3	191:3,7 201:21	305:3,8,9,14,19	57:11,22 58:21
109:20 183:4	203:5,8 204:18	306:6,8,11,12	59:6 61:11,17
184:3 301:14	205:13	307:5,21	62:8 73:10
360:13	211:15,22	308:8,11,17	118:14 258:16
cardiology 3:8	212:22 213:3,6,8	309:3,4,6	294:21,22
5:12	214:10,14 216:3	311:15,22	297:6,19 301:20
cardioprotective	219:12,21	312:3,13,19,20,2	312:10
83:12	220:3,4,14 223:5	2 313:3,5,8	carries 84:11
cardiovascular 9:5	225:7,22	314:18 315:5,16	carry 268:7
11:15,17	226:6,7,10,12	316:9,11	299:10 312:1,14
12:1,6,8,9,14	227:2 228:2,5	317:18,19	carrying 102:9
13:11,16,19,20	233:2,7	318:13 319:9,10	114:10
14:5,13 17:20	234:2,6,8,15	320:15	case 41:17 47:20
19:18 20:4 21:13	235:18	321:3,12,15	127:7 128:6
49:13,14	236:1,5,7,11	324:22 325:13	198:3 209:10
51:21,22 52:7	238:12,15	326:7 330:3	212:2 222:8,9
60:10	239:12	335:5 336:5,19	225:16 261:2
75:8,10,12,17	241:11,17,21	337:2,20 338:3,4	277:4 289:12
77:18,22	243:15 254:8	341:6 342:16	291:3 294:6
78:14,18 79:19	265:20 269:2	347:8 348:6	363:3,13
80:19 81:15	270:12,17,20	352:20 354:1	cases 69:3 117:13
83:17 84:22	271:2	care 6:17 24:16	122:9 128:2
85:6,11,12,21	272:6,7,16,18	33:2,7 38:22	139:15 140:6
87:2,5,15	273:3,6,7 275:7	65:1,6,20 66:1,4	
	276:22	96:12 134:8,15	
	277:14,17,19,21	135:3 175:15	
	279:21		

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 16

191:1,10 201:15 365:12 cash 30:12 32:14 34:20 40:14 43:20 67:17 69:2,5 casing 89:2 catecholamine 77:1 categorical 23:19 24:12 27:21 84:20 180:11 categories 36:20 45:18 46:6 117:20 158:7 167:6 190:7 202:3 347:10 category 37:18 46:4 49:7 118:3 135:20 205:1 Caucasian 273:22 280:3 causal 258:1 cause 86:12 87:5 207:7 266:7 291:2,6,15 360:10,15 caused 276:17 294:15 342:22 causes 86:16 152:9 188:17 257:15 266:6,12,20 287:22 causing 27:8 255:7,11 256:16 caveats 337:15 CDC 4:15 145:12 CDER 211:13	ceased 295:11 Cedars 5:3 Cedars-Sinai 3:4 cell 2:3 76:10 79:9,12,13 100:5 266:10,16 censor 246:6 252:20 262:17 263:20 censored 257:20 censoring 237:15,20 252:18 263:4 censorship 246:8 center 1:5,15 3:4,9 4:19 5:3 6:3 211:2 centered 254:4 centering 254:9 Centers 3:15 central 77:16 78:17 84:15 86:6 101:3 209:15 centralization 101:5 centrally-acting 26:15 cerebrovascular 273:1 291:6 certain 23:8 26:12 62:15,19 67:6 126:3 154:16 214:6 223:7 245:6 249:15 250:5 333:4,18 367:3 certainly 31:18 53:19 58:19 72:9	80:18 83:18 84:14 85:21 90:21 94:11 126:2,16 137:2 191:17 268:6 317:17 319:1 323:11 328:2 345:12 351:8 354:20 355:16 361:5,17 366:11 367:3 certainty 256:18 CERTIFICATE 370:1 certificates 291:15 certify 370:4 cetera 129:12 134:1,2,10 138:12 169:15 chair 2:9 6:13 49:2 Chairman 187:1 challenge 15:22 188:5 198:14 199:2 challenges 211:14 241:10 chance 253:22 chances 47:14 change 20:12 22:8 44:12 61:4 74:1 116:20 117:1 120:18 126:8,14 155:12 177:18 191:10,20 192:3 195:16 248:18 249:17 250:21 256:8,16 257:21 259:16 264:15 286:6 297:16	359:6 364:17 365:20 changed 56:17 144:15 350:3 changes 17:8 25:21 31:11 38:9 60:5 92:2 94:3 96:18 97:14,15 107:7 110:22 113:16 120:7 145:2,3 152:10,14,15 153:21,22 154:1,14 156:10 159:19 160:3 162:7 164:11,19 165:5,12 166:19 167:14,15 170:21 178:2 179:20 184:14 191:12,14 256:4 258:5 260:1 275:5 279:19 325:5 345:14 350:15 351:5 355:2 changing 60:1 138:20 178:17 characteristic 202:12 characteristics 46:2 148:15 159:6 286:16 291:21 299:13 300:1 314:12 characterize 252:6 characterized 22:3 286:18,22 charged 352:6 Charleston 3:21
--	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 17

charts 32:20	C-III 82:13	59:18,22 60:12	243:1,3 250:22
chief 3:14,16	C-III-containing	68:20 177:6	261:22 265:21
childhood 140:18	82:17	179:18 180:18	274:7 283:16
141:19	circle 222:2	191:6 196:22	284:7,16 285:6
children 8:21	circles 237:4	206:8 208:8,15	287:20,21
142:15	circulation 83:15	321:14 331:2	288:11,19 289:6
Chinese 138:7	86:14	352:19	292:4 293:18
choice 222:16	circumference	clearance 82:17	294:8,12 296:20
227:10,18 238:8	272:15,22	cleared 83:14	297:2,5,18 299:8
290:3,12	277:12	clearly 59:13 81:9	305:10,12
choices 215:5	citing 18:19	86:7 94:17 108:1	313:12
217:17 229:1,7	271:20	119:9 137:19	clinically 20:14
cholelithiasis	City 3:15	141:9 146:10	23:21 92:5,11
190:1	claim 34:15	154:22	121:15 159:21
cholesterol 82:22	35:4,9,15,17,21,	165:14,15	244:7 245:3
83:3,5,6 103:2	22 36:14,16 38:1	172:19 173:1	292:12 350:10
162:16,19 163:2	348:15	189:2 192:4	clinicians 52:22
164:5,14 165:2	claimed 221:11	200:17 204:12	261:9
166:3,6,9,13,16,	320:12	207:3,9 208:19	clinician's 261:16
17,21 167:11	claims 30:12	273:13 275:21	clinics 65:15 66:8
180:6 184:11,18	34:19,21 35:10	319:17 321:10	close 103:5 122:14
191:15,17,21	36:5,18,19	324:4 330:16	132:3 154:7
192:2,3 209:18	37:5,21 39:3,8	341:11 351:1	226:19 245:1
342:19 343:4,21	40:13,19	359:5	259:12
345:18	clarification 61:19	clinic 5:14 52:3	closer 200:13
cholesteryl 83:4	244:15 346:21	66:10 169:14	206:10 226:15
choose 364:20	clarify 105:15	clinical 4:11,18	231:18 359:16
choosing 181:14	240:2 243:16	6:4 15:5 16:11	closing 241:9
364:20	clarity 327:11	17:22 22:1,6	clots 86:11
chose 181:19	class 103:13	26:3,18 27:20	co 49:18 103:6
chosen 17:1	156:6,11	53:2 58:16 59:16	co-administration
181:19 183:16	classes 37:14	60:12,16 65:8	49:21
Christian 39:19,22	289:22	71:2 108:18	coal 75:2
chronic 18:7 20:9	classified 18:2	113:5 118:8	code 35:1
23:15 53:1 97:8	139:13	137:13 142:20	codes 29:20 36:11
182:14	cleaning 40:17	145:6 152:13,16	37:6
chronically 18:8	clear 47:2 48:18	182:10 183:2	co-funding 145:11
20:10 288:1		184:6 201:11	cognizant 234:1
		212:2,3 216:5	
		223:1,6 224:17	
		225:11,14	
		238:9,11 241:12	

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 18

cohort 57:7 151:19 276:7 280:11 356:15 coin 317:20 collaborate 262:10 collaboration 188:11 collaborative 188:10 colleague 58:8 colleagues 189:20 243:3 255:20 collected 137:1 collecting 134:2 138:12 280:8 College 202:8 Colman 2:22 11:4,9,10 12:19 14:2,20 71:7,8 73:12,16 106:12 243:6 260:15 270:9,10 285:13 315:22 316:6 317:13 318:18 319:6 324:11 325:10 334:12,19 335:9,22 Colman's 338:2 Colorado 5:11 combination 26:22 126:4 149:9 180:19,21 198:14,17 210:20 251:8 259:7 312:4 316:17 351:21 combinations 26:17,20 27:2,5	198:8,9,10 206:4,9 210:3 combine 198:22 199:1 206:12 combined 199:5 comes 49:9 86:2 107:13 110:2 254:10 343:20 coming 51:2 75:11 93:17 149:5 169:18 172:19 173:9 200:11 321:16 322:5 339:15 349:21 351:8 364:22 commandments 352:11 commensurate 19:12 comment 52:17 53:4 60:15,18 61:11 63:12 64:20 71:9 96:12,16 98:6 101:7 104:19 107:6 109:5 113:19 172:5 173:15 174:21 177:7 178:8 185:1 243:14 260:5,19 267:3 327:19 330:22 331:5 349:20 351:15 354:6 comments 10:9 21:21 26:5 51:17 54:8 72:18 113:12 252:22 278:3 282:4 327:7 328:1	commercial 30:11 34:20 commit 304:6 committee 1:8 2:10,12 4:8 6:16,17 7:2,7,8,11 8:1,14,17 9:10 10:14,22 11:14 12:13 15:18 18:9,10,12,17,22 51:18 95:19 171:16 175:2 271:19 286:10 294:3 296:18 301:6,8,12 305:8 311:8 313:12 317:15 325:15 326:5,6 332:8,9 341:12,18 342:7 362:19 committee's 7:16 common 49:21 71:9 86:7 95:8 101:6 109:6 215:6,21 269:5 287:16 313:2 315:3 361:10 367:16 commonly 36:11 40:2 49:15,18 92:3 213:2,7 communicated 59:11 61:6 comorbid 19:15 29:16 36:3 38:3 39:12 102:3 comorbidities 21:11 76:17 92:22 95:1,12	102:10 103:4 co-morbidities 27:18 comorbidity 16:21 28:11 companies 62:14 71:15 72:15 175:4 330:9 334:8 341:3 358:2 company 10:2 72:4 280:6 355:4 comparable 156:7 162:11 190:2 322:11 comparatively 38:19 comparator 40:7 43:6,9,14 44:5,14 45:3,9 46:10,16 303:1,2 306:5,13 310:15 319:16 320:2,3,9,19 337:4,11 353:13 compare 215:2 234:22 314:2 336:22 337:16 356:1 compared 25:21 26:20 35:11,13,18,21 38:18 90:10 98:7,21 104:14 110:12 112:10 131:17 147:6 155:3,6,14 158:16 160:11,22 161:6 163:13 166:16
---	--	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 19

170:5 179:4 189:22 194:2 202:4 221:9 248:2 261:13 280:18 283:15,21 284:16 297:15 298:2,3 306:12,16 319:7 321:4 346:8 357:9 comparing 35:16 119:20 125:18 199:11 211:21 215:7 286:16 297:8 306:8 322:16 comparison 95:3 119:20 120:22 122:6 215:4 220:16,17,20 221:1,4 246:10 comparisons 224:10 compensatory 100:1 complete 25:13 131:8 235:13,20 304:13 completed 25:17 28:5 50:6,7,14 71:21 136:17 274:9 277:8 299:15 completely 14:3 132:22 complex 289:1 296:15 compliance 7:16 8:2 258:19	complicated 111:13 complicating 296:8 complications 84:22 85:3 130:7 138:12 142:7 143:7 148:1 287:1,14,20 288:11 290:21 291:1,22 292:8,15,18 294:20 352:20 component 80:5,18 81:7 177:21 178:6 193:16 215:1 300:14 335:11 components 26:21 77:21 100:6 171:13 178:13 192:20 213:5,8,11,12,16 ,21 214:6,19,22 248:9 252:12,14 253:21 256:5 261:1,4 composed 284:18 composite 83:22 147:13,14,16 213:3,5,7,10,14, 17,18,22 214:7,18,19,20 234:15 260:20 272:7 277:3 300:6 composites 147:12 composition 26:7 177:1 178:6,14 181:1,3	compound 263:3 compounded 79:19 compounds 77:13 103:13 262:22 comprehensive 26:13 96:12 270:16 comprise 108:8 compromise 328:18 332:6 335:7 compromising 334:16 concentration 107:8 concentric 85:19 concept 87:1 239:16 332:5 concepts 211:19 219:18 307:16 concern 73:1 189:15 203:7 246:17 274:8 321:12 334:9 335:15 361:20 concerned 69:11 148:13 176:21 354:14 concerning 9:17 61:14 303:15 362:14 concerns 61:5 171:3 184:19 concession 116:11 conclude 30:1 94:20 133:10 196:16 284:6	313:13 315:19 concluded 282:1 concludes 39:18 48:21 conclusion 7:2 142:22 166:14 conclusions 159:17 209:14 218:8 concomitant 286:20 289:3 concurrency 29:16 36:17,22 37:2,4,8,10 39:3,7 concurrent 29:17,19 34:16 36:1,2,4,9 37:12,13,20 39:17 56:12 57:3 condition 84:8 209:20 321:17 conditional 239:17,18 conditions 16:15 19:16 29:16 36:3 37:18 38:3 39:12,14 102:3 143:9 207:8 290:22 357:20 conduct 208:16 303:17,20 312:22 318:8 355:11 conducted 23:7 25:2 53:7 118:8 146:22 226:9 240:10 294:18 304:11
--	---	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 20

conducting 226:2 233:17 Conference 1:15 confers 89:9 94:20 confidence 23:3 221:9,10,20 222:4 226:18 235:1,5 240:16 241:5 274:19 275:20 276:4 280:21 307:22 308:18 329:12 330:12 335:3 338:22 confirm 69:7 295:22 297:18 confirmatory 226:5 298:21 conflict 7:13,17 8:2,9 9:11 conflicts 8:6,13,18 confound 164:10 342:15 confounding 303:5 confounds 346:16 confused 14:3 confusion 219:16 congestive 36:11 37:11 39:9 85:10 90:3 147:17 Congress 8:3,11 conjecture 342:22 343:2 connection 9:12 185:6 consensus 73:15	consenting 366:7 consequences 146:2 conservative 73:6 331:20 consider 25:19 52:9 55:20 151:12 167:20 196:7 216:2 224:1 226:22 238:10 239:19 240:2 242:10 244:9 253:8 254:14 308:19 328:7 330:11 361:5 considerably 188:21 190:2 consideration 25:22 92:16 94:2,18 95:7 106:8 201:10 304:16 320:16 considerations 13:19 92:18 98:18 224:18 241:12 311:21 considered 15:17 19:17 20:18,22 23:21 24:22 41:17 42:9,12,13 44:8 110:4 126:20 151:14 152:9 182:8,15,17,19 208:2 218:10 235:3,7 242:19 286:9 301:7 305:4 310:17 311:7,9,12 343:11	considering 64:6 85:12 104:8 110:3 115:21 187:9 consist 213:11 236:2 consisted 237:7 consistent 21:10 162:21 206:21 214:21 258:7 330:12 338:11 341:17 consistently 32:18 59:21 167:8 295:5 consists 213:8 226:1 constant 225:2 233:11 242:4 293:7 338:21 constipation 202:10 constitutes 302:14 construct 220:6,17 222:11 261:8 291:22 consulting 9:1 consumed 48:2 consumer 3:19 260:22 contact 2:6 contain 250:16 contained 43:16 81:22 containing 82:14 83:7 contains 40:13	contend 107:12 content 83:3,5,13 346:22 contention 336:10 context 242:11 243:16 286:15 301:11 302:14 317:13 contingent 339:18 continue 11:22 16:16 53:15 71:19 74:20 129:15,19 130:20 168:4 208:17 212:10 265:17 268:19 278:10 315:17 351:5 363:22 continued 18:14,22 31:17 73:8 113:10 203:18 205:2,4 207:1 210:18 259:11 263:20 350:1 continues 97:11 206:15 207:6 continuing 18:16 153:12 262:12 263:2 350:4 continuous 111:8 203:19 continuously 205:22 206:3 264:22 contracts 9:2 contradictory 178:16 contraindications
--	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 21

290:5 contrast 136:14 145:22 155:20 157:19 182:6 194:7 218:22 276:2 286:21 289:14,20 313:22 337:7 contrasted 290:2 contrasting 313:13 contribute 47:10,16 86:4 289:4,10 296:9 contributed 31:14 91:17 178:2 237:7,11 238:7 242:21 contributes 81:4 293:5 contributing 47:7 90:7 contribution 110:11 contributor 94:22 control 53:17 57:14 127:7 145:21 147:4 148:1 150:2,20,22 151:3,8,11 152:10 154:1,15 155:6 160:11 166:15 167:10 168:22 169:2,4,22 174:14,18 184:11,17 190:10,11 191:13 196:12 199:12 207:5	215:3,11,16 216:10,22 217:4,8,16 220:5,10,15 222:15,16,18,21 224:16 225:8 227:5 244:10 248:18 251:21 273:16 279:14 284:22 290:9,11 293:12 294:16,19 295:2,5,9 296:2,6 297:4,14 302:15 306:9 308:5 309:12 319:15 321:11,22 322:1,3,15,18,21 323:1,7,8,16,17, 22 324:1,2,8 331:12 343:5 346:3,14 354:16 367:8 controlled 97:10 148:10 224:6 277:2 297:8 313:7 314:9 319:22 controversial 107:10,22 controversy 76:12 124:15 convene 12:12 convened 15:19 151:9 convening 7:6 conventional 124:12 converges 229:4	232:11 conversation 362:6 conversations 6:18 conversion 249:1 converted 70:1 170:11 convey 341:18 convince 139:5 convincing 75:13 convincingly 100:8 Cooper 5:4 49:3,4 324:10,11 copy 182:9 copyright 185:2 core 83:6 cornerstone 20:19 coronary 85:9,14 88:9 90:4 147:18 183:17 190:1 336:17 correct 50:12 99:8 105:10,11,14 204:14 244:17 245:8 248:22 254:12 264:11 326:10 336:21 correcting 265:14 correctly 104:21 114:1 correlated 266:10 correlation 347:7 correspond 218:18 219:8 correspondence	336:2 corresponding 220:11 221:3 corresponds 46:5 212:8 217:5,10 220:9 221:17 227:1 238:21,22 cosmetic 7:19 8:11 18:6 51:18 52:9,14 cost 66:15 133:13,20 134:13 135:11,13,17 148:3 355:4,21 costs 133:14,17,19,21 134:1,3,8 135:3,5 143:6 148:3 169:13 193:4 counsel 370:8,11 count 47:6 counted 41:21 42:17,18 236:17 237:17,22 counter 31:12 countries 272:1 country 70:7 202:18 couple 51:17 53:5 88:10 103:20 130:16 170:3 174:6 175:8 209:14 243:14 245:10 259:14 278:2 282:4 285:4 337:15 354:1 363:17
--	---	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 22

367:17 course 58:1 67:1 68:7 72:5 85:1 97:20 115:5 122:1 125:2 133:19 143:17 160:15 259:16 266:5,14 271:11 275:11 280:4 318:20 covariates 87:6 97:2 107:15 110:12 co-vary 98:12,16 cover 286:1 covered 7:17 covering 66:20 169:13 Cox 234:17 CRADAs 9:2 Craig 50:12 crazy 333:21,22 create 80:17 created 316:7 creating 134:6 creep 342:17 CRESCENDO 270:18 271:22 273:11,21 274:10 278:21 283:15 284:6,13,18,22 334:15 335:20 336:1,2,4 criteria 16:8 17:1,10 18:18 19:1 21:8 42:16 92:8 118:18	119:3 122:15 123:15 152:5 154:16 155:4 196:1 216:11 272:14 277:9 287:3 313:4 321:8 333:12 355:2,13 criterion 24:11 154:20,22 210:12 358:10,20,22 359:6 cross 127:7 crossing 138:1 crossover 264:14 265:5,7 crossovers 265:3,4 cross-sectional 98:9 117:16 crowd 109:20 crude 46:20 99:18 178:19 cumulative 29:15,21 33:21 57:3 121:19 134:11 243:18 cumulatively 34:12 cure 144:2,5 cures 144:1 curious 58:5 65:7 72:12 255:13 current 19:2,4,22 61:21 139:18 289:15 currently 22:17 24:8 52:18 60:21	75:20 107:17 114:10 293:11 302:7 Curt 2:17 360:21 curve 75:18 79:11,14 84:1 125:1 130:13 131:12 curves 44:19 203:22 274:21 275:12,14 281:3 curvilinear 78:22 79:11 197:8 cutoffs 96:1 CV 272:19 277:3 281:13,14 335:1 CVD 75:22 147:7,13 148:9,21 150:14,20 151:4,8,17 152:7 160:3 163:21 164:11 165:1 166:20 167:15 168:6 275:15,17,18 277:18 295:17 344:7,8 346:19 354:11 cycle 30:14 142:4,13,14,19 cycling 146:6 cytokine 80:22 cytokines 77:3 80:7,11,15 81:11 <hr/> D <hr/> damage 287:4 danger 364:7	daresay 13:21 dark 140:4 dashed 204:3 221:17 237:2 data 18:20 19:22 28:16 30:3,9,14 33:18 34:2,18 40:11,16,17 49:16 56:21 58:13,15,20 59:2 63:13 64:1,4,14,15 66:9 67:14 68:12 71:20 75:11 90:13 91:15 93:16,17 94:8,12,18 96:5 98:10 104:14 114:1 117:10,16,22 118:6 121:5,22 123:19 128:16 129:11 131:6 134:2 135:21 136:22 137:1,6,10,11 138:6,12,17 139:8,10 158:9 171:4 180:11 191:13 193:22 197:9,17 200:21 205:19 207:12,13 208:21 224:15 233:16 235:3 240:7,13 246:14 251:3 262:20 268:3 269:22 271:21 273:9 274:18,20 275:8 280:8,10 281:9 287:7 291:15
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 23

296:5 298:10,20 300:16 308:12 311:12 314:1 317:17,21 319:21 329:14 330:1 331:17,21 332:2 339:6 342:13 345:15 347:12 348:1,9 355:6 359:17 365:3 database 30:5,6 34:14 40:5,12,13 41:7,22 47:10,13,16 48:5 300:13 databases 63:18 dataset 41:3 datasets 68:12 date 1:10 25:12 36:15 40:18 41:13 199:11 234:14 313:18 349:15 daughter 142:9 David 4:20 28:20 day 14:10 20:3 41:12 93:17 149:22 272:4 276:13 341:7 355:1 days 40:20 41:1,8,16 42:8 43:16 44:21 45:1,5,8,12,13,1 4 46:8 48:9,11,15 303:12 367:15 day's 29:18 36:4 55:17	DCC 294:21 DCCT 295:8 de 322:16 deal 141:15 174:16 344:16 dealing 265:22 death 49:13 86:19 106:15,19 107:1 147:8,13,14 153:15 191:6 204:19 213:9 253:17 272:7 277:3 286:21 291:15 300:6 336:6 deaths 105:5 200:16 291:17 debate 99:15 213:4 322:9 362:7 decades 139:7 140:6 142:7 December 36:16 272:11 304:18 326:10 deceptive 197:9 decide 196:7 decided 12:12 129:10 146:14 152:18 decision 22:15 150:5 171:15 183:3,5 184:21 307:18 309:16 318:16 325:20 326:9 329:16 342:8 344:17 353:16 decisions 176:5	241:6 declaring 333:16 decline 193:2,6 declined 194:5 decrease 46:12 109:9 193:10 233:13 242:5 decreased 31:13 32:14 83:8 93:6,7 122:19 190:21 decreases 87:22 decreasing 224:8 dedicated 174:2 211:15,22 219:12,21 223:5 226:11 233:2 235:18,22 236:10 238:11 241:11 301:22 312:3,14,19,22 336:19 deep 86:10 defect 79:9 82:14 defects 82:4 84:16 85:21 89:18 define 16:8 22:7 143:1 212:9 223:8 236:13 238:6 261:20 292:7 defined 40:21 75:20 147:8 212:13 214:4 216:19 220:21 225:5 240:3 242:8 277:12 306:19 315:8	defines 19:7 definitely 130:2 337:22 definition 50:7 141:4 152:19 213:17 244:1 287:14 299:3 300:9 313:8 338:18 definitive 308:15 329:15 definitively 309:17 310:14 313:19 318:5 DeFronzo 263:19 degree 19:12 44:11 46:17 65:11 101:19 194:5 261:9 332:6 349:22 degrees 19:19 delay 137:16 delayed 118:10 132:5 309:18 deleterious 292:12 deliberately 338:17 deliberation 303:13 deliberations 10:14 152:17 167:2 301:10 delineated 38:5 delta 220:22 221:18 238:21,22 demand 331:11 353:8
---	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 24

Demanding 309:16 demographic 21:16 34:9,14 demographics 29:14 32:6 43:1 280:2 318:10 336:22 demonstrate 19:11 22:20 229:11,13 293:22 296:1 302:11 305:2 312:18 demonstrated 20:13 21:4 24:13,14 184:9 198:20 297:3 298:5 demonstrates 35:5 demonstrating 27:20 293:13,19 295:2 297:14 Denise 104:11 denote 42:4 215:10,14 216:1 220:22 230:5 237:1,3 denoted 225:18 denotes 46:4 dense 108:1,5,9 density 107:11 depend 212:19 350:22 366:3 depending 26:2 183:19 261:10 282:5,6,21 283:8 depends 62:5 328:10	depict 230:17 depicted 229:14 306:17,19 307:6,9 depicts 217:14 221:14 228:20 232:7 237:9 deposition 78:16 85:20 depot 77:17 78:15 80:13 deputy 2:22 6:3 derive 128:6 233:16 derived 306:15 describe 29:8,10 32:9 36:1 93:14 169:13 352:3 described 90:21 324:15 describing 49:11 306:3 descriptive 33:16 299:2 deserve 87:13 design 13:19 14:7,9 104:6 144:22 152:15 179:3 211:14 212:3 216:11 218:10 219:21 223:6 241:11 260:16 270:11 305:11 306:22 313:3 325:22 341:4 designate 59:4 designated 4:7	designed 12:8 21:6 22:7 53:6 146:19 150:13 199:14 203:6 212:1,12,21 214:18 218:4 225:22 230:4 241:8 267:22 269:6 284:8,10 299:6 312:17,18 353:20 designing 199:2 234:1 designs 212:2 225:21 264:12 265:7 269:5 312:7 325:14 desirable 103:14 desired 223:12 despite 19:22 48:11 88:2 240:18 294:10 337:10 354:19 destined 141:3 detail 89:16 96:13 124:5 182:11 213:16 223:14 227:9 details 7:1 336:14 detect 40:6 150:14 253:18 254:19 273:11 279:9 284:11 285:10 361:13 detected 41:10 detection 348:6 deterioration 194:8 302:22 303:5	determination 339:13 determinations 262:1 determine 38:8 39:16 57:6 61:17 64:14 68:12 146:1 168:5 212:5 216:4 225:13 358:12 determined 7:22 8:6 10:5 66:9 119:14 306:16 determining 224:18 245:12 333:12 Detroit 4:5 develop 15:20 79:14 90:22 142:10 205:16 257:22 344:9 developed 9:6 58:3 71:10 121:14 122:13 130:6 132:4 140:1,3 150:17 170:5,8 257:19 263:19 271:7 276:11 285:20 288:18 developing 15:13 104:18 115:4 117:13 118:4,13 123:4 125:8 141:7 187:10 195:19 201:10 288:7 300:3 304:22 development 12:22 19:6 21:18 22:18 26:9
---	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 25

59:12,17 89:11 91:20 92:18 98:4 119:10 121:7 131:15 138:10 141:22 144:19 169:21 187:12 198:11 284:3 286:9,11,15 296:21 299:15 300:22 301:12,19 303:17 304:10 310:6 311:19 315:2 355:9 devices 2:4 devoted 174:4 DEXA 26:8 dexfenfluramine 17:18 31:11 diabetes 4:14,18 5:2 11:15,20 12:1 13:13 15:4 21:12 36:12 37:2,8 39:4,10,13 55:8,9,11,13,18, 22 56:3,5,8,13,16 57:6 58:10 76:6 79:4,7,8,9,15,18, 20 85:2,4,6 88:12,20,21 93:2 104:6,8,15,19 117:5,6,12,13,19 118:4,6,9,13 119:4,11,18 121:7,15 122:7,13 123:4,8 125:5,8,13,21 126:10,21 127:1,12,13,17 128:4 130:6,7	131:11,16 132:2,4 135:8,19,22 136:11,12 137:17,19 138:17 139:14,19 140:1,3 141:2,4,7,8,10,1 5,18 142:1,5,10,13,15 143:2,5,7,10 145:10,14,18 147:1,4,22 148:5 150:1,10 153:17 154:6 160:15,17,20 161:2,6,9 163:3 169:9 170:5,9,11 179:9 188:21 189:2,10,19,22 190:3 192:22 195:15,16,20 200:8 207:9,12,14 239:13 249:2 255:8,12,17 256:17,20 257:15,19,22 258:4 262:2,4 263:18,20 266:5,8,12,20 272:20 274:3 277:15,18,19,20 279:21 281:10,12,14,17 285:17,20,22 286:3,5,7,9,13,2 1 287:4,5,8,11,13, 22 288:6,16,21 289:10,13,17,19, 21 290:8,14,15,18,2	1 291:2,5,10,13,17 ,22 292:2,13 293:1,9,10,12 294:16,17,22 295:1,16,21 296:3,12,17,22 297:11 300:18,22 301:11,18,21 302:19 304:21 305:2 307:1 309:8 310:21 311:18,22 314:15,19 315:2 316:16 319:14,17,18 320:5,8 321:14,18 326:12 355:2,13 356:5,10,17,19,2 1 359:11 diabetes-alone 281:13 diabetes- susceptibility 127:6 diabetic 46:21 55:17 57:5 139:18 140:5,8,12,17,21 141:5,6,14 142:6 290:18 291:8 321:21 352:1 359:13 diabetics 154:4 193:13 199:14 200:2 283:17 284:19 322:1 346:12 diabetogenic	103:17 diabetologists 301:14 diagnosed 121:15,18 diagnoses 34:17 36:2,9 37:8,20,21 38:1,2 39:7 55:22 diagnosis 29:19 33:12 34:19 35:2 39:3 55:8 57:3 92:8 119:3 diagnostic 138:1 287:3 diagram 79:21 82:8 dialysis 362:20,21 diarrhea 202:10 diary 175:14,16 diastolic 85:16 88:4 91:8 93:9 162:3 165:19 191:19 diatribe 197:15 dictates 63:17 die 291:14 died 191:5 diet 19:20 21:5 101:18 102:19 105:22 119:16 120:10 123:12 149:11,17 172:20 177:1 178:6,17,18 179:4 180:19,20 181:4,5,7,9
--	--	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 26

367:14 dietary 20:17 113:6 149:18 159:8 178:2,14 256:8 diethylpropion 31:16 dieting 102:21 diets 124:16 187:21 201:16 202:2 differ 140:13 166:19 180:16 271:3 281:20 312:6 differed 140:14 difference 23:14 24:4 57:13,17 69:6,8 70:6 100:12,17 123:14 124:11 131:19 140:20 159:1 164:9 194:21 196:11,15,22 197:2 215:8,12 216:8,9,16,21 217:1 219:17,19 225:5 242:9 243:22 247:10,14,15 249:6,9 250:14 254:19 295:11 323:19 337:5,8 345:20 357:20 differences 121:20 123:7,18,21 134:19 155:16,18 156:17 158:6 162:4,6,8 164:15	166:10 196:5,10 222:13 247:21 248:7,8 249:11 253:19 256:9 295:2 342:20 345:18 357:11 362:9 different 29:17 45:18 47:8 72:19 85:12 87:16 100:14,19 105:21 109:11,13 111:2 115:5 122:5 128:18 132:17 140:14,15 150:16 158:6 159:14 162:3 164:8 172:6,13 173:3 177:19 182:19 184:4 188:17 196:14 199:13 202:13 238:9 243:1 246:6 265:20 268:12 273:9 282:21 283:9 285:22 317:7 322:6 323:2,13,14 324:6 329:20 333:3 334:13 341:15 347:10 358:2,5 359:12 365:22 differential 323:6 differentially 253:13 differently 242:22 317:12 differs 225:21	difficult 51:12,13 95:3 126:2 133:20 143:18 148:14 178:19 263:6,13 264:1,5 265:5 278:12,17 314:2 337:16 351:16 difficulties 202:1 difficulty 352:13 Digestive 117:6 digits 356:12 diligence 72:3 dimension 91:8 diminution 162:22 direct 293:2 294:7 351:22 362:5 direction 25:21 54:19 58:1 61:3 257:17 361:3,8 363:11 370:6 directional 60:5 directions 26:3 78:8 directly 81:5 82:10,11 266:9 289:4,11 296:9 320:5 365:3 director 2:17,20 3:1 4:10 6:4 144:11 disability 286:20 disabling 290:21 disadvantaging 73:5 disagree 250:15 252:20	disappeared 295:12 disappointing 54:3 disclose 9:16,19 disclosures 187:11 discontinuation 72:19 236:2 discontinued 47:20 51:5 73:3 129:21 204:10 236:9 280:6 discontinues 237:21 discovered 127:5 discuss 11:14 13:10,14,15,18 18:20 238:14 260:7 304:10 311:17 325:16 discussed 6:6 9:8 16:3 19:14 22:19 61:4 98:8 184:20 294:2 296:17 301:16 302:10 310:16 317:16 362:18 discusses 152:14 182:10 discussing 6:22 7:3 14:4 144:20 discussion 6:9 14:8 28:16 54:8 73:16,21 116:5 186:12 189:6 259:4 260:11 261:19 270:4 285:8 286:7 301:9 311:8
--	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 27

316:7 325:11 338:13 340:16 351:16 352:9 360:19 363:5 368:21 discussions 8:16 10:16 334:22 disease 13:11 20:9 21:13 36:13 37:10 38:4 39:8,17 51:22 60:10 75:8,10,12,16,17 77:22 78:14,19 79:19 80:19 81:15 83:17 84:22 85:7,9,11,14 86:12 87:2,5,15 88:9,18 89:1,3,7,10,13 90:4 91:10,17,20 93:18,20 94:1,19,21 95:1 96:22 97:8 99:16 102:4 104:16 107:12 118:14 128:3,5,10 129:4,5,7 133:5 138:2,3,5 143:8 145:4 147:19,22 150:18 167:16 183:1,21 188:22 189:1,3,10 190:1,17 191:3,8 205:14 272:7,16,18,22 273:2,6,7 275:17 277:14,19,21 279:21 281:11 284:15,20 287:17 288:8 289:11 290:4	291:5,6,7,8,11,1 6,18,20 292:1,19,22 293:11,17 294:3 295:6,9,15,22 296:4,10 300:3 305:1,19 313:6 314:18 316:9 317:19 318:13 319:9 322:2 335:5 337:2 338:3,4 363:1 diseases 4:3 5:9 33:17 85:13 117:7 139:2 188:20 286:20 287:15 288:20,22 disentangle 146:11 dismiss 95:13 dismissed 98:20 104:5 disorder 18:7 36:7 37:1,8 39:6,13 286:18,21 287:17 292:2,11 disorders 36:13 39:4 84:5 286:14,17 287:6 288:9,13,18 289:1 dispensation 66:18 dispense 29:18 dispensed 29:8 30:7,20,21 31:8,21 32:9,12,21 33:1,11 38:6,11	47:6 349:2 dispensing 40:19 41:13,14 47:19,22 48:2 69:1 dispensings 40:15,22 41:3,4 43:11,12,15,16,2 0 47:9,22 displayed 355:18 disposition 79:1 235:10 236:16 266:17 distinct 314:3 distinction 20:7 285:21 distinguished 75:2 86:20 distinguishing 317:1 distribution 43:13 44:4 45:9 76:20 77:11,20 78:12 101:9 110:6 diverge 281:5 diverse 159:22 167:5 diversity 28:8 divide 230:7 divided 132:9 189:7 230:9 divides 156:3 dividing 52:4 division 2:20 3:1,11 4:11,15 5:12 11:12 12:2,4 15:10 144:11 211:12	268:10 285:17 divorce 176:1 DJD 60:11 doable 266:18 doctor 33:3 134:10 251:10 265:14 doctors 343:17 document 15:20 183:18,21 304:15 documented 27:6 38:1 141:9 338:7 345:7 done 2:5 24:7 56:10 73:11 131:11 165:4 170:20 173:12 175:6 177:4,8,16 179:6 219:16 255:6,14 256:18,21 259:9,22 263:9,22 264:13 270:13,18,21 300:12 318:9 329:6,15 344:19 365:14 dose 22:14 25:3 47:21 271:9 297:8 dose-response 22:1,7 doses 22:6,9,12 27:14 71:4 297:21 dose-titration 22:14 dosing 22:15 297:17
--	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 28

dotted 306:17,20	9:19,22	104:20	246:3,11,18,19,2
double 24:3	10:2,9,13	105:2,4,10,16,17	0 247:18
119:20 176:12	11:3,4,9,10	,18	248:14,20
297:20 355:19	12:19,21	106:3,12,13,14,1	249:4,5,14,20,22
double-blind	13:10,12,13,15,1	7 107:4,5,10	250:1,3,15
265:17 272:2	7 14:2,11,20,21	108:6,16	251:13,14,15
277:1 297:7	15:1,7,8,9	109:2,3,4,12,13,	252:9,10,22
343:16 344:16	28:17,18,20,22	20 110:14,15,21	253:2,4,5,6,20
double-mass	39:19,21 48:22	111:13,18,19	254:16,22
120:21	49:3,4,16,17,20	113:1,2,17	255:1,2,4,19
doubling 24:14	50:3,4,10,12,17,	115:3,13	256:5,15
doubt 137:17	19,20 51:4,15,16	116:2,14,15,21,2	257:13,18
downstream 84:12	52:3	2 117:2,3	258:3,12,13,14
85:2 92:22	54:5,10,11,16	144:6,7,8,10,13,	259:5
213:18	55:4,5,14,19	14,15	260:5,6,8,10,15,
DPP 118:7,17	56:4,7,9,14	168:9,11,12,13,1	18,19,20 261:18
120:6 123:2	57:2,8,9 58:7,9	4,21	262:2,6,8,9
124:9 125:5	59:7,8,9 60:18	170:2,3,7,10,12,	263:5 264:8,9,18
127:8 128:12	61:9,10	13,15,16,18,20	266:2,3
129:8,10,13	62:2,4,5,11,17,1	171:2,12,15,17,1	267:1,2,9,11,12,
130:4 131:10	8,21	8,19,21	13,14,16
133:14 135:5	63:4,6,7,8,9,10,1	172:14,22	268:1,2,8
136:14 137:13	1,22	173:1,15	269:4,7,11,17,18
138:11 143:2	64:2,3,4,13,18,1	174:6,8,9,11,12,	,20 270:2,8,9,10
144:17,19	9	13,22 175:5,8	273:17 278:3
156:18 170:4	65:9,13,14,16,17	176:17	282:12
173:5,17 176:20	,19,22 66:12,13	177:7,9,11,14,15	285:13,14,15
177:8,9,11,16,20	67:11,20,22	178:8 179:20	306:21
185:20 204:6	68:8,13,18	180:7,10	315:21,22
248:21 251:11	69:17,18,19	181:12,13	316:1,4,5 317:13
255:14 263:7	70:13 71:7,8	182:4,5,7	318:4,18
357:5 359:3	72:11	183:8,22	319:5,6,13
DPPOS 131:10	73:12,13,16,18,2	184:8,12,13,19,2	320:7,18,21
133:8,15	0	2	321:9,10,22
Dr 2:2,14,16,19,22	74:8,10,12,13,16	185:2,4,5,9,10,1	322:12,13,20
3:3,6,8,10,13,16,	,17,18,21,22	8 186:1,16,17,22	323:3,5,20
19	95:17,18	187:1 189:9	324:4,10,11
4:1,4,9,14,16,20	96:5,10,11,20	192:8 194:2	325:10
5:1,4,7,10,13,16,	97:17,18,22	200:20	326:2,3,10,13,14
19,21 6:1,3,5	98:1,9	207:18,19	327:5,6,22
	99:2,3,8,9,14	211:5,6,10	328:13
	100:10,15,16,21	243:5,7,8,10,11	329:2,18,19
	101:10,11,17,18,	244:4,15,18,19	330:3,22
	21 103:8,9,19	245:8,9,10,20	331:9,10,16,17,1

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 29

9 332:5,19,20,21 334:10,11,12,19, 21 335:9,15,22 336:8,9,13,20 337:15 338:1,5,9 339:2,5,13,20 340:14,21,22 341:9,10,21 342:4,9,11 343:10 344:20 345:1,6,9,11,14 346:20 347:2,3,4,5,6,12, 19,20 348:12,19,21 349:6,7,9,10 350:12 351:7,12,13,14,1 5 352:14,15,17,18, 19 353:13,18 354:5,17,20,21,2 2 355:7,10,14,22 357:3,4,14 358:7,8,10 359:8,9 360:12,13,20,21 361:22 362:6 363:4,16,20,21 365:10 366:3,6 367:12,20 368:9,12,14,15 draft 12:22 15:13 16:10 18:10 19:2 28:3 drafted 17:16 dramatic 121:22 122:20 129:18 231:2 351:20 366:16 dramatically 142:14 315:1	draw 225:11 drifting 180:1 drill 91:14 drive 114:9 driven 18:13 215:1 280:22 314:9 336:18 driver 159:15 drives 80:2 driving 35:6 80:9,14 82:11,13 177:21 233:15 346:15 drop 62:9 71:17 72:10 98:2 113:11 115:9 137:9 269:13 dropout 61:15 62:22 72:5 235:15 dropouts 25:1,8 dropped 269:15 dropping 71:12 drops 71:17 drove 178:1,3 Drs 28:14 drug 1:4,5 2:17 7:5,7,19 8:10 13:3 14:5,6 15:18 16:22 17:4,11,13 19:6 20:1,10,20 22:2,17 23:9,12 24:19 25:4 26:2 27:9 29:3,7,13 33:12 34:2 35:2 36:2,19,20 37:12 39:17 42:5	43:3,4,6,7,11,14 44:2,20 45:3,4,11 46:4,7,16 47:2,17 48:7,16 49:22 50:9 53:11 55:7 56:1 59:22 61:21 62:3,4,16,19 63:2,5 71:18 72:2,8,9,19 73:3,7,9 91:12 105:22 114:9,20 115:8 119:20 120:1 122:22 126:4,20,21 131:6 168:2 171:21 173:10,11,14 175:4,11 176:9 195:7,8,10,12 196:8 198:11 199:5,6,15 202:15 203:1 204:3 205:9,21 206:1 207:1,4,6 208:11,17,19 243:16 245:5 246:7 247:2,7 251:8 253:16 259:1,10 261:11,13 264:15,22 265:15 268:6,9,11,19 270:19,21 271:14,17,20 274:11 276:20 278:22 279:2,7 280:6,9,15 282:11,16,17 285:3 286:9,15 289:15 293:18 294:4,9 298:4	299:18 300:22 301:11,14,18 304:10 307:4,7 308:6,10,21 311:19 313:14,18 314:5 315:5,6 316:9 317:14,22 319:18 320:12,14 321:3 324:19 325:11 327:13 328:11,21 331:8 333:13 336:11,14,22 337:1,7 339:22 340:4,13 342:18 343:14 346:19 349:12,15 353:1,11,15,19,2 1 354:11,12 355:9,13 357:16 358:2,16,17 drug-assisted 113:16 drug-associated 49:8 drug-drug 26:18 36:1 55:15 drug-induced 284:8 drugs 1:7 2:10,12 9:6 11:15,22 12:3,5,10,14 13:1,5,7,15 15:20 16:1,7,9,12 17:16 20:7,9,21 24:8 26:6,15,17 27:3,11 28:16 29:17 34:16 36:4 40:2,7,8,10
---	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 30

43:9,22 44:6,13,14,19 45:8,9,20 46:10,11,16,20 47:1,4 48:11,13,20 49:7,9 51:19 52:22 54:1 56:2,13 60:19 61:13 64:9,12 69:5,7 70:14,16,20 71:10 91:13 94:16 98:3 101:18 109:7 111:9 114:3 115:4,14,20 124:7 126:19 136:6 143:16 175:5 187:10,18 188:1,2 194:13 196:2,3 197:19 198:12,15,16,17, 20 199:4 200:11 201:10,12 202:2,5,12,14,16 205:16 206:2,4,5 207:7,10 208:15 210:4,15,21 270:13 271:5 285:7,19 286:3 288:18 293:10,11,21 294:6 296:9,17 302:4,5,7,8 303:19 309:19 310:7 313:20,21 318:7,21 319:14,17 321:4 324:22 326:7,8 328:16 331:12 332:13 347:22 348:4 352:2 353:2 355:2	359:11 360:5,10,14 361:6,7 363:3,7 drug-use 38:22 dry 202:11 DSE 147:6 154:22 155:3 160:21 161:6,7,10,12,18 162:20 163:6,10 164:9,16 166:16,17 194:2 DSMB 150:22 due 81:18 84:17 123:22 124:1 126:1 153:15 159:2 164:11,17 166:11,17 226:16 274:8 291:17 295:17 Duke 3:7 5:18 duplicate 40:19 durable 23:15 duration 13:5 16:5,12 18:11 22:10,16 27:16 39:19,22 40:10 41:12 42:6,16 44:15,18,22 45:1,7,10,17,18 46:2,5,11,18 47:3 48:4,7,12,16,19 61:18,20,21,22 62:1,2 63:18 67:13,19 68:2,20 69:6,8,15,21 70:8,22 91:5,7 101:19 152:18 212:16 226:9 236:5,6 310:21	313:6 314:15 319:4 355:20 durations 53:14 during 7:3 9:8 16:3 31:5,6 32:3,17,22 33:6,9 35:5 38:13 40:3 41:8 47:8 54:8 56:15 66:22 68:6 102:10,11 111:1,16,22 113:20 114:18 116:5 122:13 125:4 131:2 139:13,14,21 150:8 157:4 160:7 162:8 169:7 186:10,12 259:17 260:3 267:16 270:4 275:3,8 278:6,22 279:18 303:16 304:12 305:9 328:19 368:22 dynamics 77:10 dysfunction 81:10 85:16,17 86:18 91:1 93:9 95:8 dyslipidemia 21:12 76:5 314:21 337:21 <hr/> <div style="text-align: center;">E</div> <hr/> earlier 56:17,21 59:11 67:15 71:9 91:3 143:13 169:8 171:21 190:15 194:3 195:14 197:4 206:16 207:11	210:3 225:3 230:14 253:9 255:4 273:18 278:2 314:1 330:4 349:1 363:2 earliest 88:3 early 27:5 42:3 71:5 99:1 122:2 131:20 138:16 139:6 141:7,11,13 143:9,11 150:8 162:8 200:22 201:8,9 210:9 226:8 267:18 272:13 295:9,17 323:6 331:14 342:10 Early-phase 22:5 easier 266:17 318:4 easily 327:15 342:17 eat 114:7,8 157:8 203:1 368:7 eating 157:8 175:14 eccentric 85:18 ECG 92:2,12,13 echocardiography 26:11 Eckel 10:10,13 13:10 74:21,22 95:18 96:5,20 97:22 98:9 99:8,14 100:15,21 101:17,21 103:19 105:2,10
---	--	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 31

106:3,17 107:10 108:16 109:12,20 110:16,21 111:13,19 113:2,17 115:13 116:2 189:9 342:4 360:13 368:15 economic 193:7,14 economist 135:15 Ed 4:14 5:19 editorial 82:8 331:5 education 147:4 150:1 163:4 193:1 effect 21:3 70:4,10 72:21 73:2,7 78:5 80:12 96:14 97:12 126:16 127:20 129:5 131:7 136:10 137:19 138:9 162:22 164:10 166:13 170:4,10,14,16 177:1 189:19 210:1 223:22 268:15 271:12,13 275:3,10 276:6,15 282:4 284:8 292:20 293:22 294:4 295:14 343:3 351:20 358:18,21 359:1 361:1,3 364:1 365:6 effective 25:8	53:16 54:4 122:22 123:20 124:3 170:6 179:2 199:3 210:21 effectiveness 124:8 133:13 148:3 176:6 195:13 effects 22:12 53:17 71:5 80:6 81:5 84:11 98:5 100:4 103:1,12 113:8 127:1,3 129:18 130:4,9 131:22 132:16 133:5 145:6 146:4,17 164:6 187:19 202:9,22 210:10 271:15 276:16 281:19 282:1 285:11 292:13 294:7 318:22 323:6 324:22 325:3,4 344:8 363:12 364:6 efficacy 16:8,15 17:5,10 18:13,15,22 20:12 22:20 23:7,17,19 24:8 26:19 27:7,19 51:3 61:18,22 63:17,20 66:15 73:1,5 111:4,11 176:6,8 220:6,18 222:12,14,20 224:5,16 225:21 226:1 235:11 236:3 280:16 297:5,13,18 298:5,9 304:20 357:1	efforts 21:14 eight 78:4 eightfold 314:20 either 27:21 42:12 49:16 81:10 131:6 164:1 201:22 216:13 233:4 234:15 245:16 257:17 264:14 266:11 268:9 277:14 289:4 299:11 322:13 336:15 363:21 369:2 elaborate 272:12 elderly 176:2 305:22 348:4 eldest 347:10 elected 129:19 electrocardiogram 92:6 electrocardiograph hic 106:21 electronically 370:5 element 108:14 183:15 elements 194:10 322:17 elephant 76:7,9 84:4 elevated 119:3 273:2 288:2 elevations 84:7 118:21 Eli 10:11 eligibility 41:4	118:18 eligible 119:15 Ellen 4:9 81:7 else 110:19 196:17 331:3 352:7 embarrassed 169:5 EMDAC 4:8 Emory 3:12 emotional 202:1 emphasis 173:19 346:13 emphasize 124:8 126:18 146:16 148:22 167:12 330:1 emphasizes 167:17 emphasizing 341:8 employed 10:2 370:9,12 employee 370:11 employees 7:12 8:5,12,13 employers 8:22 employing 25:7 employment 9:3 encountered 33:17 encourage 9:14 25:10 51:17 59:4 71:16 124:10 149:22 152:12 245:21 encouraged 58:22 236:12 encourages 10:21 encouraging 19:22
--	--	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 32

58:18 128:1 endarterectomy 147:19 endocrine 4:11 Endocrinologic 1:7 2:9,11 7:7 endocrinologist 3:17 15:2 endocrinologists 301:13 endocrinology 2:21 3:2,11,14 4:5 5:14 11:13 15:11 285:18 end-organ 287:4 endothelial 81:10 103:11 endothelium 81:13 endowed 103:13 endpoint 20:12 54:14,15 55:3 60:13,17,21 147:7 151:9 152:10,20 181:15,20,22 183:17 184:2,13 213:2,4,7 214:18 234:15 258:4 260:21 272:5 277:3 282:7,22 283:9 298:6,9 300:6 302:16 304:20 305:8 313:10,12 342:16 343:7 357:6 endpoints 25:18,20 26:4 73:22 181:18	182:15 203:11 204:14 213:10,18 270:17 299:5 300:10 303:10 305:20 307:1 313:8 320:22 England 192:15 English 139:19 enhance 100:5 187:19 194:16 244:2 enrich 318:9 319:11 348:5 enriched 83:2 234:6 enriching 285:9 359:15 enrichment 336:10 337:5,12,22 338:11 enroll 109:16 123:2 212:10 284:14 enrolled 118:19 123:2,5 132:3 284:18 297:10 301:1 305:19 314:18 enrollees 314:16 enrolling 276:8 305:21 enrollment 121:3 216:11 ensure 9:14 26:9 214:21 entails 305:14	enter 88:8 148:4 152:5 entered 41:22 88:17 148:16 273:5 275:13,16 entering 41:6 99:14 entertain 319:16 entire 31:6 38:14 47:21 51:10 149:2 280:11 330:11 341:8 350:14 356:14 entitle 86:3 entry 118:20 envisioned 224:12 enzyme 82:16,18 epic 236:14,15 237:8,12 epics 236:13 epidemic 70:21 epidemiological 150:16 287:7 epidemiologically 81:20 epidemiology 13:3 28:15 144:11,12 episode 40:22 41:2,6,9,11,12 42:9,11,13 44:3,6,11,16,21, 22 45:7 46:15 47:9 48:9 69:12 episodes 40:21 42:4,7,15,18 44:1,4,9,12 48:6,8 68:21 69:11	equal 24:1 215:14 217:21 220:8,9 221:2 222:10 227:4 251:19 353:5 equally 123:20 170:6 210:5 293:5 equals 224:7 equation 88:8 279:15 318:2 325:7 equivalent 119:1 121:1 125:10 173:2 215:10 218:2 227:4 228:22 303:22 ER 183:10,12 era 15:17 Eric 2:22 3:10 11:4 106:3 265:1 Erica 2:6 4:1 err 58:1 error 223:13 224:3,5,8 227:7,14 228:9 230:15 256:10 310:3 errors 256:11 especially 47:18 127:15 132:19 165:21 226:8 290:1 341:22 346:12 368:14 essence 240:7 essential 8:14 10:6 206:9 essentially 24:7
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 33

187:17 190:6 195:11 259:10 261:8 267:14 331:11 332:12 359:13 360:9 establish 206:14 207:6 297:5 298:3,4 305:7 365:1 established 297:14 335:4 ester 83:4 estimate 133:20 134:2 222:2 226:3,4 244:16 245:6 275:19 280:19 281:12 282:5,17,21 283:5 305:20 306:14 308:10 309:10 311:9 315:12 327:4,10,21 328:3,6,7,9,20 329:4,11 330:6,13,15,20 331:7 332:14 338:16,19 339:1,8,11,16 340:1 341:15 estimated 125:5 134:8 135:12 150:19 230:19 231:14 291:7 306:7 308:1 estimates 133:17 135:6,10 233:17 244:22 281:2 283:10 317:6 et 92:4 129:12 133:22 134:2,10	138:12 169:15 ethics 7:16 8:2 ethnic 21:16 28:8 123:7,14,18,22 124:4 167:5 etiology 87:4 etymological 292:6 Europe 202:18 358:14,21 European 203:7 271:17 272:1 358:13 359:2 Europeans 127:6 evaluate 10:8 15:19 129:5 183:10 192:17 210:13 238:15 240:22 299:10 311:22 evaluated 26:22 88:16,17 127:8 evaluating 11:17 14:12 23:12 62:14 285:19 306:22 evaluation 1:5 2:17 16:11 26:13,19 27:5 51:3 111:11 133:10 206:19 207:4 270:17 334:17 335:8 Evans-Watkins 370:3,18 event 23:5 148:21 150:18,20 151:4,5,6,8,15 152:7 176:10,12	201:19 204:16 212:19 213:22 214:1,4,8 215:7,9,13,20 216:10,12,17,22 217:2,3,8,17,22 218:4,8,9,14,17, 22 219:1,5,7 220:9 230:5,8,13,20 231:2,6,7,11,16, 22 232:2,5,14,16,19 237:5 242:11,12,13,14, 15 244:1,10 262:18 263:1 275:5 279:18,22 280:8 285:3 300:13 305:15 311:5 316:13 318:7 319:2 336:12 337:11 339:6 346:5,6,8 360:3,5 361:14 event-driven 212:1,7,22 event-free 215:21 events 20:21 60:7 86:13 91:17 93:18,22 96:15,22 105:2,6,12,14 129:5,7 167:16 173:22 181:17 182:3 189:16 201:12 212:8,11,19 213:7 217:6,11,15,20 218:1,15,19,20 219:6,9,10	223:8,9,12,16,20 224:9,21 226:7,16,17,21 227:8,17,20 228:1,2,5,8,11,1, 4,16,18,20 229:4,7,10,13,16, 19 230:3,7,8,20 231:15 234:3 236:8,16 237:17,21 238:5 239:6 241:7 242:21 243:19 245:13 252:19,20 253:8,13,18 254:5,17,18,19 255:15 263:3,21 267:5 272:6 273:15 274:15 276:1 277:7 278:12 279:12 280:14 300:5,15,17 301:2 305:9,14,17 306:8,12 309:22 310:1,4,5,10,11, 22 311:3 313:10 315:7,8 316:17 318:15 327:16 328:5 329:6 334:6 336:18 337:3,4,10 339:7,11 eventually 32:15 144:4 everybody 62:7 331:3 everyone 2:3,16 14:18 15:9 110:15 116:19
--	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 34

169:1 185:5 everything 102:13 352:7 evidence 75:14 89:8 117:20 137:20 155:15,18 184:16 243:19 281:16 287:4 295:7 303:22 307:19 308:15 321:15 334:15 341:5 343:6 366:22 evident 338:4 evolve 87:1 exactly 95:4 120:20 157:11 182:7,8 246:4 269:17 327:17 exaggerate 57:17 examinations 121:16 examine 63:19 231:13 284:8 examined 22:4 32:13,19 35:7 36:4,9,21 37:7 38:15 297:21 examining 145:6 146:17 295:13,20 297:16 example 12:7 24:9 25:14 26:8 37:14 52:10 57:1 60:1,22 61:2 66:21 67:6 68:4 94:3 103:2 108:8 111:5 124:22	163:10 179:21 204:10 217:3,19 218:13 219:4 221:11 226:21 228:1,15 229:9,22 231:7 232:1,16 240:3,13,22 252:16 253:14 289:7 299:12 312:1 323:9 325:2 327:12 330:14 336:16 356:9 examples 21:11 201:19 202:2 296:14 300:21 325:2 360:6 exceed 308:19 exceeding 250:5 exceeds 308:1 excellent 95:17 144:6 168:10,22 340:16 368:18 except 11:7 42:2 102:19 103:7 116:18 151:10 165:1 186:20 221:16 319:18 exception 7:9 102:5 166:21 187:21 excess 52:1,5,12 76:16 77:10 78:9 80:14 81:11 82:9 87:7 88:2 188:16 209:15 217:6,11,15,20 218:1,12,15,19,2 0 219:3,6,9,10 245:6 286:19	287:2 288:1,15,17 292:3,7,14 299:7 302:12,13 306:6 309:20 311:14 312:17 340:3 360:10,15 excesses 288:19 excessive 221:21 222:16 225:1 229:3 233:10 238:17 311:10 exclude 10:19 40:17 203:16 218:12 254:17 299:7 302:12,13 307:20 310:7,9,14,19 313:1 320:1 excluded 152:6 219:3 280:21 308:8 313:19 316:22 356:18 excludes 308:16 excluding 320:2 exclusion 10:20 execution 14:9 exercise 19:20 20:18 21:5 101:18 123:13 152:2,4,6 157:9 172:20 175:14 177:2 178:6 180:19,20 256:4,9 exercise-only 179:5 exercising 113:7 172:3,21	exhausted 41:20 exist 70:5 97:11 141:9 existed 240:7 existing 298:2 exists 106:5 241:10 expand 106:15 113:2,13 350:2 expanding 328:14 expands 80:2 expect 44:9 63:19 176:15 249:15 360:15 expectancy 191:7 expectation 176:11 expectations 57:20 expected 17:3 21:2 25:20 43:8 45:17 46:21 61:3 226:8 230:22 231:17 235:19 302:15,22 303:4 339:14 expecting 62:15 133:10 321:16 expensive 355:11 experience 53:20 61:6 110:7 114:8 133:15 215:20 experiences 71:1 89:5 experiment 365:12 experimental 104:6 256:18
--	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 35

expert 9:1 expertise 8:15 67:7 339:4 experts 301:15 explain 159:6 185:16 explained 126:16 explanation 97:16 explanations 67:4 exponential 75:19 exposed 237:2 298:15,17,18 299:18,21 300:2 314:5 exposing 262:13 exposure 141:1 236:17 238:6 273:19 274:11 279:16 280:14 298:9,13 299:12,20,22 313:6,17 314:7 315:1 355:19 expound 220:18 express 6:10 197:10 230:11 expressed 230:9 expression 197:6 extend 152:18 338:19 extended 41:15 153:2 184:13 206:22 280:1 298:8 extension 298:22 314:10 extensions 298:10	313:7 extensive 78:2 extent 45:19 89:21 98:15 128:9,13 179:6 360:14 extra 249:7 323:4 extraordinarily 113:7 extrapolate 136:22 extreme 94:2,12 96:14 extremely 61:15 117:19 209:2 244:1 351:16 eye 288:3 <hr/> F <hr/> fabulous 101:11 face 360:1 facetious 345:12 facilitated 93:3 facility 211:1 fact 44:10 52:18 68:21 73:8 76:15 81:8 83:11 86:15 87:2 98:14 99:11 121:22 127:19 133:13 151:3 178:9 182:9 187:16 196:17 204:9 207:13 223:18 224:5 226:17 234:1 239:21 240:18 247:22 281:22 291:1,7 305:1 318:6 335:16 336:4 338:7 343:7 359:14	361:17 facto 322:16 factor 95:6 99:16 233:15 234:18 251:22 265:12 277:15 288:15,17 289:12 296:8 357:11 factors 19:18 66:15 84:20,21 86:4 89:20 90:5 91:15 98:13 103:10 108:8 112:5 118:11 123:17 126:22 128:14,21 135:9 140:2 145:4 147:22 151:17 160:4 164:11,20 165:1 166:20 167:15 170:22 185:19 189:17 223:4,11,15 225:1 233:11 234:20 242:3 248:5 249:18 250:8 251:12 260:3 272:19,20 289:9 290:4 292:22 293:2 302:17 303:7 316:11 323:13 337:18 338:2 346:15 347:9,14,17 352:10 354:1,11,13,15 facts 290:13,14 failed 21:1 52:20 failing 264:15	failure 36:12 37:11 39:9 52:21 85:10,18 86:2 90:1,2,3,6 98:2 99:9 147:18 253:11,15 291:2 321:1 361:7 363:8 fair 6:8 114:5 fairly 121:2 258:7 322:6,10 357:8 fall 79:10,14 103:18 falling 102:13 falls 93:10 102:18,20 false 223:19 falsely 307:14 320:3 false-positive 92:7 familiar 120:13 187:7 family 33:3 66:2 famous 143:21 fantasy 263:15 farther 85:1 fashion 192:5 315:9 fasting 82:18 118:21 119:1,11 fat 4:13 19:8 26:10 52:1,6 77:10,12,16 78:9 87:7 101:5,6,8 102:20 120:10 124:13 177:18 178:2 189:13 209:22 256:4,8
--	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 36

257:2 286:19 fatal 96:15 147:9 190:17 252:17,20 277:4 281:1 300:7 fatality 261:3 fatigue 202:11 fat-restricted 149:16 fatty 80:14 81:11 82:11 favor 214:12 244:2 257:6 265:10 275:1,22 281:5 346:20 favorable 87:19 113:8,11 271:12 275:4 276:15 343:2,3 favorably 112:22 favoring 254:13 favours 254:2 FDA 1:12 2:5,14 6:21,22 7:22 8:4,11 10:4,18,21 11:3 12:21 13:17 15:18,21 16:10 17:16 18:9,10 21:8 24:6,22 25:19 114:22 144:11 163:19 167:1 186:9 206:16 264:13 271:18 276:21 282:15 326:8 338:17 362:8 368:17 FDA's 9:18 11:16	20:16 feasibility 223:1 224:17 309:15 feasible 224:2 226:7 310:8 311:12 319:3 feature 195:4 212:3 288:10 features 14:7 27:10 204:4 270:12 272:21 286:16 291:21 313:3 357:4 federal 4:7 6:15 7:8,12,13,16,19 8:2,5,10,13 feedback 243:4 feeding 102:12 feel 75:1 83:12 95:5 111:19 174:4 245:14 361:22 feeling 49:15,20 76:7 257:7 feels 107:18 Felner 3:10 felt 18:12 144:16 182:12,16,20,22 184:4 281:18 309:10 336:3 female 28:7 46:3 64:7 273:22 280:3 females 35:11 38:15 46:10,13 48:18 64:15 283:21 fenfluramine	31:10 259:7 fetus 64:11 fewer 44:9 161:8,12 214:2 228:11 234:7 267:5 283:20 fibrate 104:4 fibrates 103:22 fibrillation 92:19 253:15 field 73:14 107:17 128:8 183:1 192:11 263:5 265:7 351:18 fifty 310:4 figure 23:9 30:19 31:20 32:11 35:3,8,14 36:17 37:4 72:16 121:8 126:5 132:8 175:15 195:14 217:14 227:12 228:7,20 232:7 251:11 figures 190:15 192:16 198:3 230:17 filed 313:14 filing 315:5 fill 41:13 filled 43:17 47:7 final 53:4 329:16 330:22 finally 13:14 14:10 28:1 29:22 46:19 48:3,16 81:5 82:4 83:13 95:10 145:2 168:4	208:13 287:15 293:4 303:10 308:15 313:13 315:14 financial 8:6,8,13,18 9:9 10:19,22 financially 370:12 finding 258:7 266:4 295:22 305:15 330:19 345:21 366:21 fine 347:3 finish 241:9 finished 47:21 finishes 142:12 finishing 153:7 finite 200:17 Finland 82:12 firm 10:12 11:1 firms 10:17 first 2:2 12:20 13:9 15:8 26:7 29:6 41:2,14,19 43:1 47:5 50:5 61:10 67:11 68:18 71:16 83:1 100:11 120:6 127:3 130:7 131:2,13,17 138:8 144:21 147:13 151:14 157:4 160:4 162:13 172:15 182:21 185:13 188:8 192:9 194:20 222:14 226:22 233:3 235:9,22 244:12
--	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 37

245:11 265:6 268:16 270:16 273:4 274:22 275:3,9 278:3 279:18 292:11 294:12 296:11 301:17 304:19 307:3 309:15 313:20 315:15 316:5 317:9 329:5 332:11 342:14 first-line 322:8 fiscal 234:14 fish 265:21 fit 42:16 167:14 182:20,22 293:10 fitness 145:2 155:8,12 159:19 167:5 fits 362:11 five 40:8 58:11 77:21 123:5 188:16,19 280:1 297:19 310:11 fix 172:8 173:9 230:14 261:6 fixed 22:14 212:4 214:4 227:14 228:9 234:4 262:5 339:17 fixed-dose 26:17 27:2 fixing 339:15 flak 259:19 flat 259:10 flatten 131:14	flattened 131:18 flexibility 311:20 flexible 113:21 flip 257:14 262:16 fluctuated 31:4 fluctuating 31:15 fluids 87:20 fluke 338:9 fluoxetine 23:12 202:5 206:19 flux 82:12 focus 134:20 211:18 223:3 285:19 286:6 363:18 focused 124:13 351:19 focuses 149:11 folks 72:4 271:2,3 317:18 follow-up 57:12,16,21 59:8 66:12 78:4 118:15 121:17 129:6,8,13 130:11 133:22 137:15 139:12 140:5 147:10 150:15 153:2,16 168:1,16 172:2 184:8 194:7 195:17 230:2 258:13 262:21 263:2,16 279:22 280:10 295:7 font 304:4 food 1:4 7:5,19 8:10 114:14	116:10 199:6 203:1 force 80:14 333:10 Ford 4:5 foregoing 370:4,6 Forethought 22:12 forever 367:10 forget 361:15 Forgive 354:22 form 83:11 304:15 370:6 formal 244:13,14 formally 219:13 244:13 format 160:14 formed 258:15 formula 223:19 224:7 225:1 227:7 251:17,18 252:7 273:17 formulas 223:10 fortunately 334:4 forum 6:9,19 forward 6:13 25:6 57:11,22 58:21 59:6 61:11,17 62:8 73:10 98:19 Foster 193:18 Fourteen 304:1 fourth 24:15 46:6 231:5 302:6 four-year 193:22 fraction 74:2 239:5 241:7 322:18	fractional 94:5 frame 56:22 frames 56:15 framing 60:4 Framingham 170:22 171:7 314:22 France 274:6 Francisco 4:22 Frank 53:6 fraught 260:2 free 80:14 81:11 82:11 frequency 115:6 frequent 121:17 frequently 53:11 front 172:12 176:5 246:12,15 251:17,22 frustrated 137:4 full 14:17 51:10 63:2 141:9 157:22 235:14 fully-observed 42:7 function 76:22 79:9,12,13 85:22 89:18 93:10 100:12 103:11 121:13 266:5,11,16 288:5 fund 146:14 fundamental 211:19 361:12 funded 145:10
--	---	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 38

185:19 Furthermore 290:7 future 348:11 <hr/> <div style="text-align: center;">G</div> <hr/> gain 27:5,8 49:9 132:20 185:14 207:10 209:15 gained 52:11 126:7,9 154:18 158:16 165:8,9 195:9 364:12 366:11 gaining 279:5 gall 189:10 game 139:3 316:14 gap 41:16 gaps 41:1 44:8 68:4,15 gastrectomy 199:19 gastric 199:19 gastrointestinal 202:22 gather 203:4 gears 138:15,20 234:9 gee 267:17 343:22 gender 29:14 35:10 40:18 100:12 155:15 167:5 genders 188:15 gene 91:4 127:4,6 Genentech 10:11	general 9:8 10:1 19:11 21:3,8 33:2 46:21 48:20 65:21 66:2 79:6 93:13 100:22 101:22 102:1 107:17 132:15 148:1 223:21 224:20 226:14 233:6 241:20 357:1 359:2 generally 19:16 99:10 128:21 131:9 generated 353:5 generation 141:17 genes 185:20 genetic 127:3 128:9 140:2 185:15,19 genotype 127:16,19 128:3,8 genotypes 127:13 128:2 genotypic 127:20 gentle 6:11 George 13:15 262:11 264:11 357:14 358:6 363:21 365:7 Germany 274:6 gets 231:18 251:9 258:9 276:1 285:7 getting 51:8,10 124:12 132:7 138:2,3 169:17 175:4,6 245:1	254:4 278:16 327:16 333:22 359:3,22 girth 78:6 given 11:19 22:13 100:13 126:13 136:8 210:5 235:15 281:8 336:14 364:17 gives 142:5 251:8 glad 349:9 global 187:12 318:1 globally 351:10 glucose 17:8 79:14 87:12 104:16 118:22 119:2,11,12 121:14 139:21 142:2 191:18 249:2 286:22 287:2 288:1,2,17 289:12 290:11 292:2,3,5,7,14,1 6,20 293:3,4,6,19 294:11,13,16 295:2,4,8,14,20 296:2,5 297:3 302:22 303:4 304:20 322:15 glycemia 97:15 276:16 297:4 glycemic 145:20 166:15 167:10 184:10,17 290:9 292:7 293:12 297:14 302:15 308:5,20 309:12 321:5,22 322:1	323:1,8,16 328:11 glycosylated 293:14 glycosylation 352:6 goal 6:8 19:9 54:12 120:8 130:3 136:10 149:20 161:14,18,21 162:12 164:14 179:7 184:6 200:2 220:2 228:15 232:2 233:9 238:16 242:1 307:11 324:6 336:12 goals 149:19 206:10 219:12 322:22 Golden 12:21 15:8,9,10 49:5,20 50:5,10,19 51:4 54:12,16 58:7 59:10 60:18 62:2,5,17,21 63:6,8 74:8,12,16 171:21 Golden's 57:10 Goldfine 4:16 113:1,2,17 115:3 349:6,7,10 351:7,13 gone 99:15 187:5 250:11 262:21 268:17 281:8 337:3 363:7
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 39

367:14 good-bite-of-food 367:15 gotten 68:6 192:11 325:2 327:15 357:22 362:22 government 6:16 7:11 8:4,12 grade 193:21 graded 152:1,4,6 grades 193:10 gradual 120:15 130:18 154:9 gradually 149:19 grafting 183:18 grant 8:4,11 grants 9:2 graph 46:3,9 91:22 349:3 graphic 91:5 grapple 329:22 grappled 332:8 grazer 114:14 great 70:10 89:16 97:18 168:16 173:19 206:20 334:7 367:2 greater 17:11,13 20:14 21:19 24:1 34:8 35:11,12,16,19 38:17 63:20 84:15 90:9 95:7 125:7,8,14 136:9 148:6 158:2,19 159:18,20 163:3,6	165:8,15,16 197:3 214:10 220:8 221:2 239:22 240:20 248:1,4 249:2 258:17 261:9 277:10 307:5,8,10 353:21 354:3,19 greatest 127:18 133:3 152:7 160:6 162:1 green 120:17 121:9 134:18 248:5 304:5 Greenway 53:6 Gregg 4:14 57:8,9 266:2 359:8,9 362:6 group 17:14 24:2,4,19 51:9,11 52:3 57:15 58:10 66:3 79:2 82:12 94:8 119:21,22 120:17,19,21 121:9,10,11 122:10,12 123:12 125:9,11,12,19 126:6,10,15 127:9,22 129:22 130:2,14 131:2,18 132:13,14,18,19, 21 133:1,2 134:4,5,12,14 136:8,12,13 147:5 149:8,10 150:1,2,20,22 151:3,8,9,11 152:10,11 154:1	155:6,11 156:5,9,20,22 158:10 160:9,11,19 161:18 163:4 165:7,10 168:22 169:2,5 170:1 173:20 176:7 182:19 184:1,2,10 185:13 189:11 190:10 192:18 193:1,3,8,12 194:1,2,6,22 195:2 198:6 200:4,12,13,14 202:20,21 204:5,7,8,20,21 205:5,11,12 208:9,22 247:10 248:16,18 259:10,11 273:17 274:16 276:3,8 277:18 278:9,16 279:14 280:5,18 281:13,17 283:3,4 296:12 297:17 300:6 306:10 323:3,15,17 324:1,2,8 343:5 345:19 348:5,9,16 354:16,18 358:1 359:20 365:13 367:8 grouped 37:13,15,18 groupings 202:15 groups 21:17 23:14 24:5 71:12	119:16,19 120:4 121:20 122:8 123:3,5,15,16,21 ,22 124:4 131:15,17 132:10,12 133:3,4 140:13,14 141:4 156:4,6,7,18 157:7 158:22 161:16 162:11 165:12 166:11 167:6 189:7 191:14 194:18 196:20 199:18,19 200:7 209:6 247:11 251:19 282:2 284:22 316:20 322:16 323:12 342:20 348:2,10 grow 142:9 growth 3:17 31:1 guarantee 331:18 guess 61:12 62:5,11 63:1 64:5 65:11 72:12,15 74:13 99:4 108:6 200:14 207:16 226:12 240:8,12 244:19 245:21 257:13 258:22 266:18 326:17 329:2 330:22 331:1 342:14 350:3 352:18 353:18 354:7 guest 10:4,13 13:9,15 Guettier 14:11
---	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 40

285:14,15,16 316:1 320:7,21 321:22 327:22 329:2 336:13 337:15 338:5 339:2 355:22 guidance 11:16 12:1,3,22 14:12,15 15:13,20 16:11,19 17:15 18:10 19:3,4,7 20:7,19 21:9,14,22 22:22 23:18 25:1 26:7,16 27:12 28:3 56:16 57:10,20 58:11 60:20 61:21 62:13 72:13 111:6 262:3,4 286:2,11 297:1 298:11 299:16 301:1 304:15,18,19 305:5 306:2,7 307:2 310:6,12 311:16,18,19 313:15,16,17,21 319:14 320:5,8,13 321:14 326:11 330:10 356:10 guidances 59:11 guide 128:10 guidelines 17:22 18:2 20:17 21:11 52:18 202:7 GXTs 346:10 gynecologists 33:5	<hr/> H <hr/> half 28:5 43:6,19 44:2 45:11 47:14 48:9 64:8 120:15 130:12,22 132:3 136:18 145:7 150:15 153:3 179:14 180:5,9 198:8 252:1 272:3,4 274:15 280:13,15 298:19 358:18 359:13 Hamman 256:3 Hampp 28:14 39:19,21,22 49:17 63:22 66:13 67:20 68:18 69:20 70:13 Hampshire 1:16 hand 6:18 49:1 308:7 handle 25:1 188:4 handled 303:5,9,11 handout 82:6 hands 95:20 hang 108:22 110:12 happen 114:5 205:18 334:5 346:4 364:10,20 happened 42:22 69:2 144:18 257:20 262:18 355:3,12 364:11 366:9 367:4	happens 118:1 132:18 157:16 158:9 159:1,16 happier 354:20 happy 95:15 142:19 182:11 183:22 184:21 211:3 333:2 354:3 358:9 hard 51:3 60:7 134:18 173:16 244:1 257:3 262:14 265:13 351:17 352:2,11 356:1 harder 74:7 hardly 208:6 harm 12:9 17:20 20:5 254:17 281:7 320:15 362:15 Harvard 4:10,17 52:2 187:5 hate 144:3 haven't 58:22 137:1 157:22 165:4 169:6 170:7,9 173:12 180:10 254:14 265:11 340:3 having 70:7 84:16 94:6 128:3 152:7,9 155:1,4 166:12 168:19 258:18 266:13 326:21 334:22 341:5 354:6 357:18 362:21 366:10,16 367:15	hazard 88:11 125:8,9 215:17 234:17 235:1 273:12 274:18 275:19 276:3 279:10 280:20 281:12 282:8,17 283:1,4 284:12 306:14 307:6,9 313:19 333:5,7,14,17 hazards 215:17 HB1c 295:12 HDL 82:22 83:2,5,8,11,14 162:16,19 166:3,5,16 167:11 184:11,18 192:3 HDLC 271:12 276:15 head 4:4,17 5:2 144:1 171:11 337:16,17 headache 202:11 headway 71:22 health 30:4 31:10 46:21 48:20 52:15 70:11 78:4 91:9,15,21 135:15,17 148:1 187:16 193:7,13 194:11 209:16 287:18 291:1 293:3,22 healthcare 30:6 135:10 143:6 193:4 healthier 151:18 346:10
--	--	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 41

Health's 34:13 healthy 88:12 297:11 hear 85:1 104:21 184:19 203:4 262:6 264:4 362:8,13 heard 53:4 71:14 120:12 136:15 143:13 187:17 194:14 197:20 253:9 268:4 287:21 289:17 290:13 300:5 306:21 327:7 333:21 hearing 20:2 331:2 heart 15:4 36:11,12 37:10,11 39:8,9 59:19 75:15 85:9,10,14 86:2,22 88:5,9 90:1,2,3,6 92:6 93:10,11,13 94:9 98:2,6,10,17,19, 20 105:18,22 106:7 109:8,9,18,22 110:1,3,10,11 138:5 147:18 170:14,17,18 171:9 190:1 253:11,15 275:17 276:19 291:5,6,8 321:1 324:16 361:7 363:8 HeartLab 107:20 heavier 140:11 367:18	heavy 140:17,18 366:17 height 141:21 held 6:7 11:13 225:2 He'll 13:11 help 66:13 118:2 128:10 149:18 183:4 185:11 254:5 261:22 324:18,20 338:20 341:2 342:8 helped 315:20 helpful 178:7 261:3 helping 350:10 helps 172:2 247:19 Helsinki 82:12 hemoglobin 19:11 54:20 148:10 160:4,7,8,10 161:14,20 165:6,12,14,17 179:22 200:3,5 271:13 293:14,15 295:3 297:4,16 304:19 Hemphill 49:17 Hence 146:14 Hendricks 5:19 51:15,16 106:13,14 354:21,22 355:10 Henry 4:5 hepatic 188:22 189:3	hereby 370:3 here's 82:6 85:14 89:3 124:22 166:3 hereto 370:12 heritage 141:9 he's 260:16 Hi 5:16 61:10 Hiatt 5:10 59:7,8 96:10,11 170:2,3,10,13,16 ,20 171:12,17 243:10,11 244:15,19 267:1,2,11,13,16 268:2 269:4,17,20 316:4,5 318:4 319:5,13 320:18 341:10 high 13:1 24:20 39:2 52:21 55:7 57:12 61:15 96:1 117:20 118:2,12 119:7 123:13,17 142:18 167:18 198:4,16 202:15 203:12 205:16 208:9 209:18 235:11 250:4 289:9 292:16 295:16 300:2 301:2 308:4 312:14 314:21 317:11 325:17,18 332:11 333:1 343:21 345:5 346:8 360:3 high-density	191:15 higher 18:21 36:21 37:7 46:10 69:5 88:5,6 90:16 96:4 123:8 126:10 127:12 140:8 158:21 188:21 214:1 218:9,19 234:6 235:15 242:13 285:10 313:5 315:1 316:14 330:16 339:11 343:4 347:15,17 348:21 357:12 higher-risk 312:10 361:2,15 highest 21:18 53:10 117:20 121:9 123:4 134:5,13 135:3 224:1 250:10 277:17 279:22 316:18,20 highlight 304:5 highlights 241:4 highly 84:1 108:17 121:21 151:15 183:19 208:2 250:18,20 287:6,15 293:1 high-risk 123:16 127:16,19 128:3 136:1 316:15 317:2 319:11 335:1 336:16 362:2,14 hint 344:20 Hispanics 123:9 historical 222:21
---	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 42

224:15 historically 115:14 histories 35:1 history 14:14 114:11 144:18 148:20 173:10 272:16,18 273:5,7 274:1,2 275:17 277:14,20 279:20 284:20 314:17 317:19 319:9 337:2 338:2 363:14 hit 13:1 143:22 260:15 hoc 300:14 hold 105:20 holding 233:10 242:3 home 193:5 homer 99:10,19 homozygous 127:10 honoraria 169:16 honorarium 169:12,16 honorariums 169:10 hope 144:4 187:8 196:6 349:12 353:13 354:9,12 hopeful 176:16 hopes 366:12 hoping 15:22 148:8 hormone 77:9	horrible 175:20 323:18 horse 362:3 hospital 4:5,12 34:21 hospitalization 147:9,15 181:15,19 184:16 193:5 213:12 313:9 321:1 hospitalizations 134:10 147:17 148:2 153:1 hospitalized 152:20 174:20 176:11 182:12,14 183:7 184:5 hour 116:21 186:7 house 79:5 hsCRP 84:7 273:2 huge 245:12 human 107:14 humans 365:11 hundred 310:4 hung 340:22 hunger-motivated 114:9,14 hungry 114:7,13 hypercaloric 102:12 hypercholesterolemia 274:3 Hypercoagulation 108:10 hyperglycemia	294:15 hyperinsulinemia 99:22 hyperlipidemia 255:9 hyperproduced 100:2 hypertension 21:12 36:12 37:9 39:4,13 76:5 81:6,15 86:3,14 90:4,8,12,15,19 91:11,12,14,16 93:1 95:2,4 97:8,9,10,12 102:5,7 189:22 255:8 274:3 314:21 337:21 346:3 356:19,20,21 hypertriglyceridemia 108:3,9 hypertriglyceridemic 104:1 hypertrophy 85:17 86:1,17 89:17 hypoglycemic 150:10 Hypopnea 194:4 hypotheses 307:3,15 hypothesis 118:9 142:4 147:5 152:21 153:1,4 182:22 220:7,11 221:1,4 223:18 224:4 243:17 244:13 267:22 307:3,7,11	343:19 hypothesized 140:22 hypothetical 41:22 236:22 329:21 hypoventilation 86:6 HzR 216:1 <hr/> I <hr/> i.e 216:8,9 224:3 225:5 228:21 233:7 241:22 242:9 ICD-9 29:19 34:22 36:10 37:6 I'd 2:2,5 11:4 54:5 59:10 66:12 116:15,19 153:11 157:12 160:3 164:18 172:14 173:15 178:8 182:11 183:22 184:21 196:14 243:2 264:4,21 313:13 315:19 331:5,7 334:11 340:19 350:2 358:4 368:13,16,20 Ida 3:19 idea 63:17 100:3 106:20 137:15 176:6 260:21 261:2 296:20 350:9 ideal 82:1 identical 247:22 316:20
---	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 43

identification 18:1 identified 352:12 identify 2:5 22:8 ignore 84:5 ignores 292:21 ignoring 268:13 II 2:18 75:13 83:11 156:6,11 III 81:22 90:12 IL 77:2 ILI 154:21 155:2,5 159:18 160:22 161:4,5,17,19 162:14,19 163:4,6,13 164:9,16 166:14,17 ILI/DSE 166:10 ill 146:9 I'll 14:19 15:15 84:13 92:10 105:14 129:6 134:21 144:20 145:1 177:18 188:6 189:14 193:16 196:6 197:16 198:12 212:9 213:13 220:18 223:8 230:14 246:20 247:18 253:7 273:8 277:21 285:11 343:11,12 360:21 365:7 367:20 illness 53:2 144:2,5 146:10	illnesses 287:19 illusions 355:17 illustrate 216:17 217:12 236:20 293:10 300:21 illustrated 221:12 294:11 illustrates 23:9 28:1 240:22 313:16 illustration 41:1 221:6,14 222:6 237:1,9 illustrations 218:7 237:13 illustrative 326:22 ILS 120:2 125:11 I'm 2:9,19,22 3:3,6 4:1,20 5:4,7,16,21,22 6:3 15:1,3,10 50:1,12,17 54:13 57:19 58:5,7 64:4 65:20 67:20 68:18 70:22 75:1,4,5 79:21 88:10,20 89:15 90:14 94:3 95:14,15 96:6 97:15 100:7 101:12 104:6 105:20 113:2,3,21 114:10 115:2 117:3 120:5 124:5 131:5 135:14 136:1,2 138:19 139:7 142:19 144:10,21 153:9	158:8 160:13 164:21 165:3 168:18 170:15 172:16 174:9,17 175:20,22 176:1,2 177:5,12 179:18 181:16 183:11 187:7 196:3,4,6 199:9,10 206:15 211:3,11 247:4,5,9 249:8 253:12 255:13,19 263:7 264:11 270:10 271:1 281:6 285:16 293:8 296:19 309:13 331:1,2,6 334:19,21 335:5 336:21 338:15,16 339:15 340:5,11,12 343:5 345:11 347:2 349:7,9,11 350:5 351:19 352:9 354:5 358:8 359:9,21 362:5 image 293:17 imagine 281:7 342:16 343:6 355:15 imbalance 342:13,17 343:1 imbalances 337:9 immediate 294:14 immediately 112:9 immobile 193:3 immunizations	135:18 impact 70:8,20 88:20 168:6 184:9 190:22 191:2 192:22 193:14 214:8 227:11 236:16 241:16 248:4 251:11 253:12 260:3 287:21 288:2 291:1 293:2,3 313:16 320:6 338:4,11,12 355:8 366:10,16,19 impacted 256:4 impacts 229:15 288:6 impaired 79:14 104:16 119:1,2 249:1 impairment 314:21 356:8,11,16 impairments 305:22 imparted 107:7 108:7 imparting 108:14 imperative 213:1 imperfect 353:2 implement 12:3 implementation 296:22 313:15 implemented 14:15 239:18 241:3 300:10 311:18 313:4
--	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 44

356:18 implication 327:19 344:5 345:21 implications 167:1 194:12 213:19 223:15 233:5,19 343:13 346:17 implied 91:3 97:19 172:15 implies 224:9,21 364:3 implying 103:16 227:4 importance 189:16 261:4 important 13:21 26:19 55:1,2 61:7 79:2,17 81:12 91:19 95:2,4,6 98:13 102:16 105:19 107:11 115:12 133:6 141:19 150:4 152:8 164:10 168:17 169:17 178:13,22 188:22 192:6 193:11,16 194:9,11 197:12 201:10 207:3 216:2 235:9 238:10 239:19 243:12 248:17 251:6 254:20,21 292:12 294:12 309:15 315:14 322:2 325:6 350:11 365:19 importantly 75:16	91:1 impose 334:17 impossible 126:2 impressed 352:9 impression 348:3 improve 135:8,17 293:12 347:10 354:13 improved 60:3 103:11 112:5,9,12 128:20 166:17,20 194:11 308:5 345:13 347:13 354:2,11 367:5,8 improvement 19:12,17 93:9 102:8 155:14 160:10 192:10 220:2 221:7,8,11,13,16 222:7 224:21 228:21 229:8,11,13 232:8,18,21 233:4,9 241:19 242:2 254:8 266:20 295:1,3,4 296:1,5 297:3 347:8,16 improvements 20:1 25:19 101:14 128:22 145:19 155:8 161:19 162:1,2,19 163:3,5 165:1 166:1,5,8,15 167:10 352:22	353:4,10,15,22 improves 209:17 improving 294:15 354:15 imputation 25:7 impute 58:12 imputed 8:19 10:18 62:10 IMS 30:4 inactivity 91:19 inadequate 308:6 inappropriate 53:3 inappropriately 209:21 incidence 19:21 23:4,5 117:13,18 121:19 122:7 125:13,21 127:17 130:5 131:11 136:12 143:4,7 147:7 179:9 191:1,8 195:16 204:16,19 205:10 274:16 280:17 283:3 284:21 285:5 306:8,13 include 8:22 18:18 21:12,15,18 22:6 33:2,7 34:22 41:4 59:5 66:2 92:6 134:9 152:20 213:5,16 236:1 238:2 252:17 304:5 313:5 325:7 included 16:13	40:1,7 42:7,16 43:2 47:14 66:5 85:8,9,10 152:21 176:21 203:14 238:4 272:20 284:19 301:13 302:18 includes 50:11 147:14,16 149:8 188:11 213:21 282:10 including 8:20 15:6 26:14 30:11 38:7 40:14,16 45:14 52:3 56:20 57:5 66:15 76:22 77:16 93:1 138:11 147:22 210:20 219:17 324:8 335:4,6 inclusion 272:13 277:9 279:20 inclusive 213:14 inconsistent 276:16 inconsistently 337:13 incorporate 224:9 234:19 237:15,20 246:1 incorporates 224:12 increase 23:4 27:6 52:7 72:8 83:3 87:20 90:11 103:16 105:22 106:5,7 108:9 109:5,7,10,18 110:5 149:19 188:14 190:3
--	---	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 45

209:16 223:21 227:2 228:5 245:5 272:15 277:12 281:17 305:3 307:5,8,20 308:8,16 310:7 313:1 314:8,14 324:16 328:17 330:13 355:20 363:10 increased 18:5 32:15 38:11 44:11 45:17 46:17 75:17 76:16 81:18 84:21 94:20 107:7 146:7 164:2 166:18 174:19 189:2 253:16 258:16 271:16 272:22 276:19 280:22 286:20 295:18 296:1 299:9 305:18 306:17 308:2,9,13 310:20 313:6 314:6,8,16,19 315:1 318:5 324:13 330:12 337:10 increases 12:6 88:4 92:6,21 93:12 101:4,7 146:19 188:8,15 223:20 227:20 228:11 231:1,19 233:12 236:4 242:4 276:17 287:16 288:7 310:18 increasing 77:15	84:6 92:21 109:22 142:15 176:16 183:11 189:21 328:5 336:12 346:13,14 increasingly 67:17 incredibly 95:6 174:2 243:12 indeed 279:17 309:20 independence 108:20 independent 89:9 90:4 92:22 110:11 305:7 313:11 index 29:11 33:14,22 78:6 79:2 117:15,18 118:2 119:5,8 194:4,8 266:18 indexes 199:15 Indian 117:9 138:18 141:10 Indians 117:14 123:9 139:9 142:18 indicate 38:2 44:19 71:3 237:4 indicated 40:9 42:3 45:10 48:3 59:13 117:5 238:12 293:12 indicates 126:9 indication 48:12 51:20 130:15 296:21 indications 20:6	37:12 56:11 indicators 179:17 indices 96:13 140:9 indirect 294:7 individual 26:21 108:7 145:18 149:8,10 171:13 210:4 214:18 252:12,14 287:3 290:5,10,22 291:9 292:8 300:14 311:6 366:20 individuals 6:10,11 16:20 18:19 19:15 71:14 75:14 90:9 109:16 145:14,17 146:22 147:2 148:4,16 149:14 155:22 156:1,12,14 157:2,4,19 158:13,15,18 160:9 163:11,17 188:12 191:4 272:3 273:5 275:15 276:7 280:9 282:16 285:10 287:12 290:9,16,17 305:22 312:10 313:5 314:6,13,14,20 315:2 335:13,14 364:3,14 366:18 individual's 8:7 288:7 291:8 industry 5:22 7:9	9:18,21,22 10:1 inevitably 128:5 infant 142:6,8 infarction 92:9 213:9 300:7 infarctions 190:18 Infectious 4:3 5:9 infer 137:10 223:22 352:3 inference 68:17 inferences 225:12 inferior 92:8 inferiority 222:20 inferred 140:22 inflammation 89:21 inflammatory 76:5 81:11 83:19,22 84:8 103:12 influence 22:15 103:10 127:1 128:2 143:9 293:6 influenced 223:4 information 7:15 10:5 16:18 33:16 34:10,14 41:5 45:6 47:17 64:10 96:4,6 128:9 174:13,18 187:9 197:10 212:4,8 216:5 219:15,17 222:21 223:2,7 227:13 237:11 266:19 285:22 286:5 324:14 347:21 348:1
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 46

355:14 356:22 information-based 212:2,3 223:6 informative 92:14 112:1 246:8 252:17 informed 24:18 informing 296:15 inherently 314:2 inhibitor 276:11 inhibits 82:18 initial 85:7 129:22 156:5 160:2 167:7 199:21 200:20 201:7 203:22 205:3 211:18 259:8,22 260:4 264:12 initially 85:17 87:19 88:6,11 159:11,13 204:2 218:20 236:8 269:9 273:11 367:6 initiating 21:22 Initiative 91:10,16,21 innovative 293:20 input 12:12 243:3 261:22 325:22 358:8 insert 203:13 inserts 115:1 insist 175:2 353:9 insisted 332:7 instances 209:17	353:3 institute 4:2 5:2 15:4 117:6 122:4 129:12 institutes 5:8 145:11 institutions 187:8 instructed 60:16 insulin 57:5 59:20 76:1,2,13,22 77:5 78:21 79:4,7,8,12 80:5,8,9,12 81:2,4,7,9,14,17 82:3,10,22 83:16,21 84:10,14 87:10,14 90:19 94:22 99:6,7,11,12,16, 17,19,22 100:1,4 103:10 108:22 112:8 142:1 145:20 148:7,12,13,19 155:18,19 161:10,11,12 191:18 266:7,9,12,15 289:20 294:16,17 324:9 insurance 43:18 66:20 69:1 intake 20:18 91:18 114:15 159:8 256:8 integrate 170:21 integrated 59:21 170:22 integrates 30:9	intended 19:6 34:3 75:11 211:16 intended-use 318:17 intense 358:12 intensity 357:21 intensive 120:1,7 122:18,21 124:2 134:6 145:7 146:18 147:3,6 149:1,12 150:9 151:6 154:2,12 155:10 156:3,20 157:13 160:5,9 162:9 167:2,3 168:6 169:22 184:10 193:8 194:1,5 255:10 350:13 357:9 intent 182:21 286:5 intention 282:10 intentional 19:20 146:2 intention-to-treat 280:16 282:9 interact 289:11 293:3 interaction 26:18 66:19,21 68:1 76:4 281:20 317:2,4 interactions 173:20 289:5 interest 7:14,17 8:2,9,19 9:11 10:19 23:5 32:7 34:11 36:20 37:6 41:10 187:4	225:8 305:15 313:11 363:18 interested 55:6 101:12 182:2,5 216:18 217:19 225:17 253:12 360:21 370:13 interesting 96:20 188:5 191:16 194:3 204:4 207:21 366:14,21 interestingly 97:4 191:21 275:1 interests 8:22 9:10 10:7 174:3 intergenerational 139:11 interim 224:13 245:16 275:7 329:5 intermediate 134:4 135:4 intermediate-sized 82:2 intermittent 210:20 intermittently 187:14 205:22 206:3 internal 33:4 66:3 303:6 internet 185:6 interpret 55:14 56:10 113:15 115:8 174:15 248:19,20 250:13 268:3 278:12,17 317:9
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 47

327:21	133:4,18 134:7	investigated 46:1	98:19 100:10,22
interpretable	135:11,13	investigation	103:21 104:4,19
99:18	137:16 138:10	100:9	152:14,15 173:4
interpretation	143:16 145:8	investigational	187:9 216:2
213:19 255:21	146:18 147:3,6	297:9,21	246:11 250:2
258:2 336:21	149:1 150:9	298:1,14,15	254:10 259:16
interpreted 55:10	151:7	299:18 306:9	279:7 283:10
66:1 136:21	154:2,13,15	314:5 323:7	328:10 332:22
137:10 234:13	155:11	324:9	362:19 366:2
317:10	156:4,13,20,22	investigators	issued 9:12 34:4,6
interpreting	159:21 160:5	150:7 203:11	304:15 311:16
115:11	162:9 168:6,20	273:15 275:2	issues 6:9 9:8 16:3
interprets 114:1	173:14 184:10	279:13 280:7	26:5 61:5 88:8
interrelationships	250:7 253:16	344:10	90:7 94:13,17
108:20	255:10 256:21	investments 9:1	185:2 234:10,11
interrupted 40:22	257:8 258:5	invited 9:18 183:3	241:15 286:8
interruption 6:11	259:2 295:10	involuntary 313:7	296:15 301:9,16
interstitial 87:20	344:22 345:3,7,9	involve 10:16	344:17
interval 68:15	349:17 350:13	involved 15:3,5	it's 15:11 24:16
92:7 93:11 94:9	353:14 354:8	175:13 352:10	51:3 55:18
111:22 112:14	357:8,11,16,18	involvement 10:20	59:9,17,22 60:11
221:9,10,20	interventions	involves 9:4 80:16	61:6 64:16 65:5
222:4 226:18	113:7 127:2	IR 99:19	66:9,10 70:18
235:1,5 240:16	130:4,10 132:6	Ireland 274:6	73:13 74:22
241:5 274:19	134:15 143:3	irrelevant 251:1	76:8,9 77:21
275:20 276:4	155:21 167:3,20	316:10 334:1	79:2,17 95:3
280:21 307:22	175:10 255:10	ischemia 89:17	96:20 98:15,20
308:18 329:12	357:10,19	183:21	100:9 102:13,20
330:13 335:3	interview 175:22	ischemic 36:12	104:3 106:18
339:1	364:19	37:10 39:8	107:15,22
intervals 111:15	intramural 3:18	isn't 181:2 365:3	108:21 111:13
intervene 363:2	intrigued 338:15	368:4	112:9,11 115:17
intervention 24:17	introduce 2:13 6:2	Israeli 88:15	126:2 132:5
113:14 115:15	14:21 28:19	issuance 11:16	133:20 140:10
119:22 120:2	117:11 144:8	299:15	141:12,13
121:11 123:1	199:8 211:19	issue 9:17 11:2	145:10,13
124:9 127:9,20	introductions	26:16 73:14 97:8	146:16 149:12
128:7,13,14,20	187:3		154:19 157:2
130:1,2,17	inverse 271:7		162:14,15
	investigate 106:20		163:18,21 166:1
			168:19
			169:13,15

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 48

171:20 175:16 180:18 181:3,22 187:2 188:13 191:5 194:22 195:1,15 197:8 199:2 204:6 206:8 207:18,19 213:1 222:10 236:10,15 238:5,10 242:11 246:1,5 248:11 249:6,7 251:6,9,10 252:1 253:22 255:5 256:19 258:6,7,9,20 260:21 261:20 262:14 263:6 264:1,5 265:5 266:21 278:15 318:4 322:4,14,21 323:5,17 326:22 328:10 329:6 330:18 331:18 333:21 334:9 337:4,16 340:2,10,11 344:13 349:4 351:17 352:2,10,19 353:7,17 354:9,10 356:1 359:18 361:2,6,9,11,17 363:5,9 366:5,8 367:16 368:5 IV 183:13 I've 82:6 90:20 112:6 117:8 138:18 143:13,15 167:12	173:11,12 188:9 189:6 192:11 195:17 199:10 201:13,18 202:4 206:4 208:13 253:7 255:3,9 265:10 274:13 282:8 327:7 333:20 352:15 364:2 Iyasu 144:8,10 <hr/> J <hr/> Jack 3:16 JAMA 105:9 Janet 370:3,18 January 36:14 105:9 277:8 Jay 92:4 Jean 285:16 Jean-Mare 14:11 Jefferson 2:6 28:21 Jensen 5:13 262:8,9 264:10 347:19,20 348:19 Jim 260:22 job 280:7 John 5:16 Joslin 4:18 Journal 192:15 journals 128:19 252:18 judgment 208:17,20 223:2 224:17 340:7	Judith 3:6 Julie 12:21 15:10 July 272:13 294:2 296:18 301:5 justification 184:15 justified 336:3 <hr/> K <hr/> Kaplan 44:16 Kaplan-Meier 204:13 274:21 275:12,14 281:3 Kaul 3:3 103:8,9 104:20 105:4 181:12,13 182:5 183:8 184:8,13 260:18,19 262:2 330:3 336:8,9,20 338:1,9 339:13 Kenchiah 52:1 kettle 265:21 key 124:9 169:19 216:16 220:20 222:13 241:15 244:8 246:11 286:8,13 kick 344:3 kidney 117:6 138:4 288:3,5 291:2 kids 141:2 143:11 kilogram 154:8 195:21 209:5 248:16 kilograms 119:6 120:22 148:20 191:22 197:1	198:3 201:5,6 268:22 kinds 60:11 188:2 259:19 268:3 Kluwer 34:13 40:11 knowledge 53:20 151:10 Knowler 13:12,13 116:15 117:2,3 144:7 168:12 170:7,12 173:15 177:9,14 178:8 207:11,18 255:4 256:6,15 257:18 259:5 266:4 342:5 357:4 358:7 368:15 known 37:13 61:13 75:15 216:10 218:4 222:18 270:18 277:20 291:22 293:14 Konstam 3:8 61:9,10 62:4,11,18 63:4,7,9 72:11 73:13 260:5,8 326:13,14 327:6 328:13 329:19 330:22 331:16,19 339:20 342:9,11 344:20 345:6,11 Konstam's 71:9 Kramer 3:6 Krauss 87:3 <hr/> L <hr/>
--	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 49

label 18:16 138:2 195:18 labeled 37:16 103:15 labeling 260:9 laboratory 107:13 lack 12:8 18:19 236:3 339:21 lacking 296:7 laid 253:8 254:14 Lamont 3:13 large 11:19 15:5 75:14 83:11 109:16,19 125:3 128:20 146:4 170:1 188:18 225:13 233:5,6,19 241:21 254:18 288:6 290:1 294:18 312:19 322:18 329:8 349:22 366:19 367:4 largely 131:20 larger 38:19 160:21 224:22 233:9 240:12 242:2 256:9 310:5,11 315:6 361:8 last 13:7,15 14:10 25:6 41:12,13 48:1 57:11 61:11,16 62:8 71:14 73:10 74:5,8 80:1 130:16 133:13 196:13 239:16 244:15 285:4	364:21 367:10 368:13 lastly 138:15 227:5 234:3 243:2 late 53:1 92:19 139:3 196:13 311:16 latent 262:22 later 20:3 32:5 56:18,22 74:19 88:18 110:18 112:11 139:22 186:3 198:13 220:19 226:5 239:11 255:17 260:15 262:7,18 263:3 288:21 365:20 367:7 late-stage 296:20 Latter 93:17 Laughter 14:1 175:7 368:11 Laval 86:21 laws 7:14,17 8:3 LDL 102:17,18,20,21, 22 103:1 107:8,9,11,15,18 108:1,5,9 163:2 164:5,14 165:2 166:6,8,11,13,17 ,19,21 192:2 325:17 342:19 343:3,20 344:12 345:4,8,10,18 lead 31:7 38:14 211:11 288:4 290:21 leader 58:10	285:16 leading 84:21 201:16 291:2,6 lead-ins 278:18 leads 121:19 292:3 294:12 296:6 301:5 360:7 lean 26:10 leap 359:10 learn 110:7 185:16 learned 14:15 89:4 338:1 least 16:13 24:3 25:3,4 27:18 28:11 34:6 90:15 98:2,3 112:1 118:10,19 119:5 120:8 128:3 132:5 141:16 142:11,17 148:8 155:1,4 158:2 167:21,22 169:19 175:2 183:18,20 192:19 246:22 249:13 272:19,20 275:4 298:15,17,18 299:17,20 310:4 322:17 324:2 333:15 341:6 352:19 355:19 359:17 leave 14:19 282:3 285:11 leaving 41:7 316:3 363:19 LeBlance 196:12 LeBlance's 247:19	led 11:16 117:22 118:6 124:20 125:16,20 142:3,14 144:19 206:17 276:13 277:16 279:19 280:19 325:5 left-hand 132:8 Leibel's 364:9 length 42:20 197:21 lengthening 176:13 leptin 77:1,7 365:17 less 10:12 18:16 58:12 73:9 83:2,10 86:7 92:11 101:1 107:2 110:1 148:11,12 154:5 157:8 161:15,20 162:10 165:11 169:5 183:16 199:11 200:22 201:1,5 208:4 220:12 221:5 233:8 239:2 241:22 247:1 267:15 274:14 280:13 285:7 323:16 329:11 330:16 344:21 345:2 361:10 363:10 366:20 lesser 128:21 lesson 207:3 let's 72:19 76:18 81:16 240:2 261:14 344:2
---	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 50

<p>364:11 368:4</p> <p>letter 212:9,14</p> <p>level 43:10</p> <p>80:16,17 101:22</p> <p>138:1 189:1</p> <p>207:22 224:7</p> <p>302:14 305:3</p> <p>306:17,19</p> <p>357:13</p> <p>levels 37:19 75:19</p> <p>81:3 155:8,12</p> <p>158:21 195:11</p> <p>271:12 288:2</p> <p>347:16,17 352:5</p> <p>liability 26:14</p> <p>lie 225:9</p> <p>life 63:20 121:8</p> <p>131:12 136:11</p> <p>138:16 139:22</p> <p>141:7 143:9</p> <p>148:2 187:15</p> <p>191:7 203:11</p> <p>347:22 367:14</p> <p>lifestyle 20:16,22</p> <p>21:5 24:17</p> <p>56:18,20 112:17</p> <p>113:6 115:15</p> <p>119:22 120:1,7</p> <p>121:10</p> <p>122:19,21</p> <p>124:1,2,6,8,21</p> <p>127:16,19</p> <p>128:13,19</p> <p>130:1,17</p> <p>131:6,18 132:21</p> <p>133:4 134:5,6,14</p> <p>135:4,11,13</p> <p>137:15 138:9</p> <p>143:3,15 145:7</p> <p>146:18 147:3</p> <p>149:1 150:9</p>	<p>151:6 154:2,13</p> <p>155:11,21</p> <p>156:3,13,20,21</p> <p>157:13 160:5</p> <p>162:9 167:2,20</p> <p>168:6,20 169:22</p> <p>173:14 175:10</p> <p>176:22 184:10</p> <p>187:19 193:8</p> <p>194:1,6,17</p> <p>195:13</p> <p>196:12,15,16,20</p> <p>197:1 203:18</p> <p>205:11 208:22</p> <p>209:9 210:1,10</p> <p>248:2,3 249:12</p> <p>255:10 278:5</p> <p>344:22 345:3,7,9</p> <p>349:17 350:13</p> <p>353:14</p> <p>354:8,12,13</p> <p>357:8,9,11,16,19</p> <p>,22 358:12,14</p> <p>364:18</p> <p>lifestyle/placebo</p> <p>194:21</p> <p>lifestyles 359:2</p> <p>lifetime 42:21 48:6</p> <p>288:7</p> <p>life-year 135:13</p> <p>light 302:20 309:9</p> <p>357:18</p> <p>likelihood 75:17</p> <p>76:16 84:16,21</p> <p>90:12 241:1</p> <p>likely 20:11 67:8</p> <p>77:9 82:19 141:1</p> <p>142:9 151:16</p> <p>159:11,13</p> <p>161:21 204:6</p> <p>291:14 331:12</p>	<p>335:3 363:14</p> <p>365:15</p> <p>Lilly 10:11</p> <p>limb 291:3</p> <p>limitation 40:10</p> <p>300:16</p> <p>limitations 29:22</p> <p>47:5</p> <p>limited 7:17 20:2</p> <p>47:11 48:4</p> <p>233:16</p> <p>289:18,19 290:4</p> <p>331:17</p> <p>line 153:22 154:1</p> <p>204:3</p> <p>208:2,3,4,5</p> <p>221:17 268:21</p> <p>306:18,20 331:5</p> <p>linear 96:3</p> <p>linearly 191:10,19</p> <p>192:5</p> <p>lines 73:20 121:12</p> <p>204:15 217:16</p> <p>237:1,3 275:1</p> <p>281:4 349:3</p> <p>link 81:9 90:3</p> <p>linked 35:2 168:19</p> <p>292:16</p> <p>linking 75:21</p> <p>links 34:19 83:16</p> <p>lipase 82:15 83:9</p> <p>lipid 36:7,13</p> <p>37:1,8 39:4,6,13</p> <p>81:16 83:15</p> <p>85:20 107:17,21</p> <p>163:7,9,12,15,22</p> <p>164:3,4 256:6</p> <p>344:8 351:19</p>	<p>352:5 363:8</p> <p>lipid-lowering</p> <p>351:21 361:6</p> <p>lipids 17:9 19:10</p> <p>54:20 59:20</p> <p>97:14 145:19</p> <p>256:12 259:17</p> <p>346:13</p> <p>lipoprotein 82:15</p> <p>83:9</p> <p>lipoproteins 81:19</p> <p>82:5 108:12</p> <p>352:6</p> <p>liraglutide 319:20</p> <p>341:10</p> <p>list 25:18 60:11</p> <p>85:14 86:16</p> <p>92:10 171:5</p> <p>186:3 189:6</p> <p>261:1 269:19</p> <p>listed 93:4 128:19</p> <p>198:1</p> <p>listening 187:3</p> <p>lists 189:5</p> <p>literature 17:6</p> <p>78:3 122:15</p> <p>little 17:6 28:4</p> <p>43:5 59:10 74:7</p> <p>84:13 86:15 88:5</p> <p>96:2 97:7 106:15</p> <p>120:3,18 122:6</p> <p>130:15 131:19</p> <p>134:18 135:11</p> <p>137:20 138:6,14</p> <p>139:4 140:20</p> <p>172:3 177:19</p> <p>178:15 180:16</p> <p>192:12 197:15</p> <p>208:6 246:6</p> <p>260:16 266:3</p>
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 51

268:19 274:14,21 275:19 279:13 280:13 309:13 317:6 323:5 324:2,18 328:14 343:12 345:11 354:5 365:21 lively 99:14 liver 77:16 80:3,8,10,15,17 82:11 189:10 living 263:14 loaded 102:20 local 80:11 303:9 344:11 locally 80:16 Location 1:12 LOCF 58:12,17 59:4 74:1,7,10 logical 288:9 long 16:1 27:1 49:22 53:16,17,21 54:2 67:5 113:10 130:4 131:3 159:12,13 199:6 205:20 234:19 275:4 303:21 355:12 367:11 longer 44:8,9 45:8,19 46:11,17 48:11,14,16 53:14 63:21 67:2 115:21 162:6,15 164:6 215:21 236:6 237:16 281:8 345:4 longer-term 130:9	138:8 longest 44:16 45:7 46:15 48:9 longevity 98:22 longitudinal 34:18 117:16 138:18 139:9,10 140:1 longstanding 102:7 295:21 long-term 19:8 24:22 40:6 52:15 118:15 130:4 131:7 136:7 137:21 145:6 146:1,17 167:9,19 168:5 180:20 191:7 293:22 295:7 303:4,17 304:7 321:2 351:6 358:3 Los 3:4 5:3 lose 24:1 118:3 120:22 125:11,12 148:14 149:14 158:18 159:11 165:13,15,16 166:5 181:6 185:21 191:22 205:12 209:8 259:11 267:5 268:4,5 275:22 279:6 349:13 350:6,8 366:13,18 losing 17:12 102:22 111:20,21 113:6 137:3 146:9 157:2 174:17	180:11 279:4 343:17 loss 11:22 16:9 17:4,11 18:4,6 19:7,8,13,16,20 20:8,15,21 21:2 22:12,20 23:11,12 24:8,10,11,22 25:20 26:10 27:3,9 49:7 54:14,22 55:7,12,21,22 56:7 57:16,18 59:13,15 60:14,17 65:15 66:8,10 70:1 74:3,6 94:2,7 96:14,19 101:13,16,19,20 102:12 109:6 110:22 111:1,7,8,16 112:2,9,21 113:8,11,15,20 114:2,19 115:5,9,14,15 119:7 120:9,13,14,15 121:7 124:9,11,22 125:1,4,6,7,15,2 0 126:1,4,16,20 130:5,10,15,18,2 0,22 131:4,6,7 132:7 133:2 136:6,8,9 137:2 143:17 145:13,16,18 146:2,6,19 154:3,5,8,12 155:16 156:17 157:15,21	158:3,7 159:5,9,10,17,20 160:2 164:21 165:22 166:12 167:9,19 168:3 170:4,10,14,17 174:15 177:1,17,22 178:2,3,11,13,16 ,17,20 179:2,7,8 180:9,15,18,21 181:10,11 187:16,18 189:18 190:6 191:9 192:7 193:11,22 194:11,15,16,22 195:1,21 196:4,8,9 197:3,5,7,10,13, 14,18 198:18,22 199:18 200:7,19,20,22 201:2,4,6 203:22 204:1,2 205:9,21 206:7,10,14,17,2 0 207:7,11 208:10,11 209:2,5,16,21 210:2,11,12,18 211:17 248:1,10,12,13,1 7 249:3,10,16 251:1,6,9 253:10 255:7,16 256:19,20 257:15 259:15 260:4 261:12,15 263:7,9,22 264:20 266:20 268:18 269:1 270:21 271:10,11 276:14,15 278:7
--	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 52

284:9 288:4,5 335:21 336:1 343:22 344:2,3 347:8,14 349:14,18,19 350:5,11,16 351:6 352:2,21 353:5,10 354:3,10,12,19 364:1,9 365:2,5 366:16 367:1,2,9 losses 146:4 154:7 156:8,9 157:10 159:22 164:22 166:8,20 167:7,9 197:16,22 357:19,22 lost 125:14 126:7,11 131:2 137:3 150:11 153:14 154:18 155:1,4 156:20 157:14,20 158:4,8,10,19 165:9,11 169:6,18 179:15 185:13 194:1 195:10 196:21 199:20,21 201:5 204:1,8,12,22 205:6,8 246:22 263:10 267:4,20 279:1 350:18 367:4 lot 50:21 57:16 77:20,22 84:11 85:5 88:7 90:1,6 93:3 102:8 123:2 124:15 126:16 128:15 137:18 157:9 172:22 180:17 185:16	197:20 258:3 260:2 267:4,20 268:4 281:15,18 321:1,16 329:1 341:20 353:19 356:6,22 363:17 364:6 lots 249:21 266:6 269:5 love 264:4 low 28:12 32:18 37:2,9 39:7 54:2 55:8 117:19 135:15 151:7,14 174:14 198:15 226:9 244:1 281:22 300:18 317:1 low-calorie 187:21 low-carbohydrate 179:4 lower 18:20 31:18 44:19 51:20 101:2 118:3 126:11,14 128:7 136:13 189:1 190:2 194:6 198:8 199:17 219:1,9 224:20 234:8 242:15 256:4 291:3 300:19 316:15 329:3,13 330:20 360:5,6 365:18 lowered 127:15 lowering 18:18 103:12 294:11,13 295:14,20 363:8 lower-risk 276:3	335:13 361:4,10 lower-than-expected 279:17 lowest 127:17 134:4,14 135:4 156:9 316:17,19 low-fat 179:3 low-risk 317:11 361:13,18 362:17 LPL 82:16 lumped 57:4 lunch 7:4 116:9,12,21,22 186:2,6,10,12,15 LV 93:8 Lx 34:13 40:12 Lynn 4:13 <hr/> M <hr/> MACE 213:8,10,11,14,2 1,22 214:1,2,6 234:15 252:13 253:9 272:6,10 273:12,16 274:16,18 277:3,6 279:10,14 280:17 281:9 282:9,22 283:1 284:9,12,22 285:2,5 300:4,5,8,14,17 302:16 313:9 315:8 319:2 macronutrient 181:1,2 macrovascular	133:7 295:6,14 Mads 5:21 9:19 magnificent 199:4 magnitude 164:20 165:22 166:8 310:5 339:18 mail 40:16 mail-order 38:7 main 27:10 32:7 mainly 14:7 maintain 149:15 167:21 290:11 350:10 367:2 maintained 121:2 131:1,20 155:7,13 157:22 158:2 159:20 160:9 350:15,16 maintaining 111:7 154:11 157:21 maintenance 20:8 109:8 111:2,10 130:5 143:17 162:2 179:16 180:20 181:11 major 14:7 16:4 94:22 95:2 97:5 137:19 146:12 163:18 189:2 190:22 193:13 213:6 241:19 270:11 272:5,19 273:14 288:10 300:4 305:9,13 306:8 366:10 majority 18:17 28:7,10 32:4 38:15 43:15 53:11,14 64:6
---	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 53

158:4 290:17 300:2 304:5,11 354:2 males 35:13 284:19 manage 141:17 335:20 managed 123:16 303:8 320:4 323:12 management 15:14 20:19 107:21 322:2 managing 324:6 mandated 109:15 manifestations 138:3 manifested 89:18 manner 16:17 55:15 276:6 manners 85:19 mantra 156:12 March 1:10 277:8 Mare 285:16 margin 218:11 219:2 220:22 221:3,5,18,20 222:5,9,19,20,22 223:14 224:14,19 225:5 226:15 227:1,10,15 228:3,6,8,11,14, 18,22 230:21 231:10,14,18 232:1,3 233:11 235:2 238:18,21 239:1,2,4,6,9,10, 14,15,21	240:1,3,4,5,17,2 1 241:2,6 242:4,8,10,14,16 243:20 244:3 254:6 306:18 309:14,15 310:16,19 311:14 329:11 margins 224:20 226:19 238:19 242:10 262:4 310:17 mark 42:3 marked 353:22 marker 84:7 markers 83:19,22 111:4 market 17:18 31:3,7,9,13,15 36:20 38:14 200:12 321:13 327:13 marketed 302:7 marketing 301:3 308:12,13 309:2,5 325:5 Marv 3:8 331:10 Marvin 334:5 Mary 2:19 322:13 329:9,17 360:22 363:4 Maryland 1:17 masked 129:17 151:9 mass 19:9 26:10 29:11 33:14,22 78:5 82:10 93:8 94:4 117:15,18 118:2 119:5,8	189:11 199:15 matched 190:10,11 material 285:21 286:6,8 340:16 Matt 13:18 211:11 279:15 matter 51:1 57:21 58:2 140:10 238:5 330:18 331:13 334:9 matters 9:7 370:8 max 155:9 maximal 22:11 23:10 120:14 251:9 maximally- tolerated 22:9 maximum 74:6 154:3 155:8 249:10 may 8:22 11:1,7 19:20 24:6 26:11 37:17 38:2 47:18,22 63:18 66:22 67:6,9 70:9 76:8 77:17,19 81:8,22 87:19 93:2 100:5 102:5,7 105:11,14 106:20 109:7,8,10,13,21 110:3 111:8 115:4 116:18 128:6 144:2 146:6 152:6 173:9 181:17 186:8,20 188:4 197:6 204:9	209:20 213:18 223:22 233:21 235:12 238:1,9 242:22 259:4 260:15 275:10 279:4 283:9 290:1 293:2 314:16 318:19 320:3 324:7 338:9 341:14 343:22 344:2 357:14 361:7,10 362:1,2 363:13 365:4,8,10,18,19, 22 367:10 maybe 54:16 61:2 66:13 73:21 97:10 111:6 114:22 172:6 175:4 244:7,22 245:1 246:4 254:18 262:9 267:19,21 269:7 326:15 327:7,11 329:9 331:2 334:21 337:6 338:20 354:1 356:14 363:6,21 365:7,19 367:17 Mayo 5:14 52:3 McAfee 4:13 95:21,22 96:8 176:17,18 177:12 178:5 179:11 180:4,8 367:12,13 meal 149:17 158:20 350:21 mean 17:10 23:17 24:9,11 27:21 28:6,9 45:7,17 51:11 61:20
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 54

62:1,13 72:14,15 73:22 96:3 105:20 108:17 115:7,19 118:20 119:8 120:7 128:4 137:21 165:6 170:8 173:17 178:16 182:16 196:10,22 197:2 201:4 247:21 248:7,8,12 249:6,9,11,16,18 250:1,9 253:22 257:13 259:12 261:7 263:15 265:3 266:6 269:12 273:21 274:1,10 280:2,14 308:3 314:15 317:7 326:16,17,19 328:15 332:3,17,22 334:8 335:16 337:22 339:20,22 343:11 344:10 349:11 352:1 353:18 356:2 362:16 365:8 meaning 139:19 205:1 238:11 meaningful 23:21 216:7 244:8 245:3 305:20 meaningfully 318:8 means 41:17 63:7 172:16 181:9 193:20 240:11 257:9 353:11	359:21 meant 72:13,17 128:5 213:15 mean-weighted 196:5 measurable 349:22 measure 46:21 48:20 55:2 59:16 99:10,19 100:17 102:21 112:15,19 114:19 178:19,20,21 183:7 215:4,5,22 216:4,14 218:6 219:19 256:1 257:4,5,6 292:5 297:4 316:13 353:17 measured 25:16 26:8 59:21 74:4,5 117:15 119:12 137:11 257:16 272:15 measurement 73:11 103:3 256:7,8,10 measurements 25:11 26:7 50:8,15 51:2 99:5 102:9 111:21 114:18 115:11 256:7 265:12 measures 58:19 142:1 147:20 151:13 162:17 163:21 169:20 178:14,20 211:21 259:20	266:14 276:16 367:3 measuring 107:18 256:12 mechanism 26:2 86:2 101:16 198:20 266:19 324:13,19 325:1 mechanisms 81:8 89:15 90:2,18 95:10 109:11 mechanistic 90:5 mechanistically 81:21 82:19 93:2 media 6:20 7:1 median 43:14 44:5,13 45:10,17 130:10 295:16 Medicaid 30:12 32:18 34:21 43:21 medical 3:4,9,15,20 4:10,17 5:3 15:10 18:5 19:7,8 23:15 37:21 39:15 79:6 133:14 134:8,15 135:3 199:13,21,22 200:4 208:20 322:7 medically-treated 200:12 Medicare 30:11 34:20 medication 26:1 27:7 34:16 37:1,14 38:13	55:9,17 57:7 112:16 150:5,8 160:17,20,22 161:2,4,6,8,20 162:7,10 163:20 164:3,11 166:19 167:14 173:9 174:15,17 200:6 208:1 210:6,7 262:19 264:3 269:3 289:22 344:9 346:16 medication-associated 27:4 medications 14:13 18:4 31:16 36:6,7,8 37:1,3,16,17 38:21 39:6,10,11,15 49:10 55:11,12,21 56:5,7,12,13 57:5 66:14,20 67:5,18 68:11 150:10 151:17 160:15 161:9 163:7,9,12,15,18 ,22 164:4 200:10 201:15 209:21 210:1 262:12 290:2 344:18 349:2 medicine 3:7,14 4:10 5:11,14,17,20 33:3,4 66:2,3 75:5 135:16 192:15 323:1 medicines 134:10 203:7 271:18 meet 24:10 152:4
---	--	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 55

175:21 221:12,22 239:4,6 240:17 241:2 312:4 315:17 327:8 341:6 meeting 2:11 6:6,8,14,19 7:1,3,6,20 8:16 9:8,9,13,20 10:1 11:5,6,14,16 12:12 15:21 16:4,10 19:2 116:5,16,17 119:3 133:6 154:16 186:12,18,19 214:12,16 224:13 267:17 270:4 286:10 294:3 296:18 301:6,8 311:8 316:8 326:5 330:18 366:8 368:22 369:1,5,6 meetings 150:2 158:14 169:18 176:3 351:2 meets 221:21 287:3 Meier 44:17 member 116:6 270:5 369:2 members 6:17,20 7:10,11,22 8:1,17 9:10,11,15 10:15,16 18:12,17 103:20 116:4,9 186:11,13 187:2	270:3 301:8,12 304:1,2,6,9 368:20 men 88:15 100:10,14,20 155:17 188:14 189:22 318:12 menopause 78:15 mention 11:11 137:12 mentioned 33:8 34:1 60:9 105:17 106:14 110:22 174:14 193:15 225:3 244:8 254:12 312:16 322:1 330:3 337:18 341:10 mentions 39:1 menu 181:18 menus 149:18 mercury 276:18 message 128:1 330:17 met 184:3 299:19 313:20 320:13 328:4 340:1,9 meta 202:6 301:20 306:4 312:9 meta-analyses 250:2 meta-analysis 196:13 247:19 249:20 305:13 312:2 metabolic 1:7 2:10,11 7:7 19:18 76:3,8,11,12,20	77:20 80:1,19 84:3,5,6,9,11 89:20 107:6 112:5 189:8 272:21 289:1,2 352:1 metabolically 112:7 metabolism 2:20 3:1 11:12 15:11 100:3 285:17 292:2 meters 119:6 metformin 56:19 57:6 119:21 120:19 121:10 122:17 123:20 124:1,2 125:19,20 126:2,12,14,15,2 0 127:14 128:14,21 129:18,19 131:2,5,17 133:3 134:4,13 135:4,6,19 143:3,16 170:4 207:12,22 255:11 319:19 322:8 method 32:13 136:22 330:11 methodologies 107:19 methodology 234:16 methods 29:9,17 32:10 124:12 306:3 MI 28:12	147:8,13,15 190:17 204:17 252:16,17 253:16 272:8 274:2 277:4 281:1 336:6 mic 349:9 Michael 5:7 Michigan 4:6 micro 133:7 microphone 256:14 microvascular 290:20 292:17,19 294:20 295:4 microvasculature 288:3 mid-1990s 289:19 mid-90s 18:3 87:3 middle 132:13,22 134:13 176:1 201:22 318:19 Mike 5:13 76:15 263:5 264:10 milligrams 272:3 276:13 278:5 millimeters 276:18 million 32:2 34:22 35:1 38:12 40:14 43:2 70:15,19 290:16 mind 34:4 49:9 77:19 78:11 87:9 92:13 126:19 196:7 236:15 275:6 315:14 343:15 345:14
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 56

minds 129:3 mine 197:15 minimal 111:20 127:9 minimum 274:12 299:19 319:2 Minnesota 5:15 minor 8:20 98:16 minorities 148:18 minority 123:3 148:8 minus 41:13 85:18 215:11 217:2 minute 129:6 132:8 160:13 180:14 203:3 267:3 276:20 minutes 124:19 149:20,21 187:15 257:1 270:11 mirror 209:18 293:17 misinterpreted 105:12 misleading 92:15 317:5 miss 52:5 249:10 missed 47:9 179:13,19 missing 58:13,15,20 59:2 73:7 Missouri-Kansas 3:15 mitigate 188:6 205:15 210:19	mitogen 100:4 mixed 20:2 68:22 mobile 192:19 mobility 192:10,13,17,21 193:3,6,10 194:9 model 126:9 234:17 292:1,9,21 293:4,11,16,17,2 0 294:1,3,11 modeled 108:19 125:4 195:15 197:5 248:3 modeling 125:6 126:3 234:16 248:21 255:14 models 234:18 292:10 moderate 37:2,9 39:3,7 124:19 356:11 modern 15:17 modest 19:19 104:14 110:12 113:7 120:11 125:20 131:5 166:20 167:9 342:21 modestly 112:9 modifiable 87:4 118:10 modification 20:16 21:1 52:20 56:18 108:11 112:18 184:17 278:6 352:6 modifications 21:5	83:19 107:8 modified 77:19 84:20 94:6 112:22 115:22 modifies 103:6 modify 80:12 83:5 94:13 102:2 110:3 210:17 modifying 80:7 81:2 96:19 moment 90:8 185:22 195:3 199:5 272:12 273:10 277:22 momentarily 80:4 money 134:16 135:7,9,12 monitoring 115:7 122:1 129:11 357:7 monotherapy 198:19 298:1 month 113:10 149:4,6 172:4 207:14 265:4 366:9 monthly 30:10 33:15 months 25:15,17 45:21 62:3,9 63:2,3 67:2 68:5,15 73:11 102:14 111:7,8 112:6,11,18,20 115:16,17 119:12 120:14 130:18 149:4,5 201:1,4 205:3 210:8,9 236:3	268:16,17,18 269:1 274:11,12 278:6 279:18 281:5 298:5 344:3 364:21 366:7 368:1 morbidities 103:7 144:5 189:4 morbidity 19:9,21 54:13,21 145:8 146:7,21 168:7 188:9 morning 2:2,8,16,19 3:3 7:5 15:9 28:22 39:21 75:1,6 117:3,4 136:4,16 187:3 189:9 192:9 206:16 287:22 290:13 342:2,10 347:21 350:12 354:7 359:18 369:1,4 mortality 19:9,22 54:13,21 75:18 91:11,18,21 93:16,20 94:1 97:1 98:22 99:1 104:22 105:1,3,13 130:8 138:12 145:9 146:8,21 168:7 182:18 188:9,13,15,16,1 9 189:3 190:8,14 191:4 200:16,18 204:15 291:12 295:18 296:1 328:17 331:21 340:4,12,13 mostly 38:22 48:8 67:16 255:5,9
---	--	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 57

273:22 280:3 298:22 mother 142:6 176:2 mothers 140:8,12,17,21 141:18 143:11 mouth 202:11 move 32:9 86:16 206:9 276:9 moving 149:20 359:15 364:5 multicenter 145:5 146:17 194:19 multicentered 118:7 multifactorial 95:9 multiple 47:22 224:10 235:3 287:19 289:3 multiplicity 86:4 235:4 308:1 Multiplying 212:15 muscle 80:7 89:22 100:5 myocardial 85:16 89:17 92:8 95:8 190:18 213:9 300:7 myocardium 85:20 89:19 93:4 myocyte 89:16 myself 135:15 176:21 244:20 mysterious 248:11	mythical 102:1 <hr/> N <hr/> nail 144:1 namely 217:17 227:13 310:17 narrow 328:5 narrower 226:17,19 narrowing 327:16 national 4:2 5:8 30:5 33:19 58:14 70:20 117:6 nationally 40:16 nature 76:10 240:9 nausea 202:11 NDA 62:14 307:19 328:19 331:21 NDAs 330:2 nearly 30:15,16 35:1 159:20 192:4 209:3 near-maximal 22:11 Neaton 260:22 necessarily 52:13 59:4 64:16 172:18 199:3 323:18 325:15 333:10 necessary 8:14 241:12 326:18 331:4 340:10,11 necessity 183:14 negative 58:17 60:1 98:11	negligible 70:21 337:6 negligibly 337:13 neither 299:6 370:8 nerve 288:3 nervous 361:17 neuronal 276:10 neuropathies 89:20 neuropsychiatric 26:13 271:15 325:4 nevertheless 87:16 Newcastle 75:2 NHANES 90:12,14 NHLBI 183:4 nice 63:13 78:22 166:4 206:20 nicely 204:1 328:19 347:6 NIDDK 15:2 night 84:16 NIH 3:18 15:2 17:21 20:17 21:10 145:10 146:14 176:20 nine 67:1 nitroglycerine 183:13 nobody 164:1 333:2 no-effect 22:8 noise 214:7,11,16 254:3,8,11 256:6	328:6 noisy 253:22 nominally 322:14 non 9:20 140:5 141:5 147:8 155:19 163:14 221:21 222:15,20 224:22 229:3 233:10 277:3 281:1 292:21 300:6 353:10 non-blinded 199:12 non- cardiovascular 317:22 non-clinical 26:17 299:8 non-diabetic 117:15 118:1 122:12 139:17 140:4,21 141:12 non-diabetics 283:17 none 164:8 203:12,13 262:14 269:21 non-excessive 220:16,20 221:1,15 222:1,8,11 224:19 232:10 233:4 234:21 238:17 241:19 242:3,6 254:3 non-fatal 96:16 147:8,13,15 204:17 213:9 252:16,19 261:1
--	--	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 58

272:7,8 277:4 281:1 300:7 non-glycemic 137:21 non-inferiority 220:17 222:12,14 224:16 298:4 333:11 non-smokers 75:15 non-traditional 289:8 non-traumatic 291:3 noon 116:21 nor 10:14 299:6 370:8,12 Nordisk 5:22 10:3 norepinephrine 276:10 normal 87:12 90:17 93:12 100:3 139:20 291:9 319:7 normally 71:21 notably 271:15 274:9 note 116:19 144:3 163:16 195:1 198:7 199:17 208:1 209:1 214:17 218:16 222:1 238:1 267:8 287:10 326:19 368:12 noted 10:21 61:1 219:18 323:15	notice 131:21 283:18 noticed 177:4 179:12 noting 213:17 222:10 236:10 242:12 363:5 notion 264:13 November 274:5 Novo 5:21 10:2 N-times-T 212:17 nuances 320:11 null 182:1 220:7 221:1 223:18 224:4 307:3,6,11,14,15 number-of-events 227:11 numerically 245:4 nurse 33:8 66:5 Nurses 78:4 nursing 3:20 193:5 <hr/> O <hr/> Oak 1:12,15 obese 11:20 17:7 19:14 27:17 28:10 39:2 70:17 87:11,14 88:5 92:9 106:1 119:9 138:22 140:18 145:9 155:22 156:1,6,11,14 190:9 191:11 194:10 200:15 287:13 347:13,15 364:14 366:18	obesity 3:17 5:2,20 9:7 12:3,5,10,14 13:1,5,7,11,12,1 6 14:5,6 15:17,19 16:1,7 17:16 18:1,2,7 19:21 20:6,8,10,19 21:17 22:2,17 26:6,17 27:11 28:16 34:4 36:14 39:15 48:11 49:22 52:22 53:8,18 54:1 58:10 66:8 70:4,6,9,16,20 71:10 72:2 75:7,10,20,22 76:15,17 78:17,18 79:20 80:20 81:17 82:3,21 83:16 84:19 85:13 86:4,10 87:2,4,6,10,19 88:7 89:7,8 90:3,16,19,22 91:6,7 92:2,3,12,14,17, 21 93:1 94:15,17,19,20 95:11 97:21 98:4,8 101:6 102:4 106:22 107:2 108:2 109:22 112:5 117:4,12 118:11 126:19 138:17 139:2 141:3,15,19 142:22 143:9,20 187:4,10,15 188:8 189:5 194:13 198:12	199:16 206:12 207:9 209:18,19 210:7 238:13 243:16 265:7 266:5,8,15 270:13,19 271:4,8 272:14 276:12,21 277:11 285:3,7 286:5,7,12,18 287:5,9,13,15,21 288:15 289:10,16,18 290:3,14 318:7 319:14 324:22 342:18 346:19 349:2 359:11,16 360:4 363:3 obesity-related 21:11 object 251:2 objective 214:9,13,16 220:1,2,13 221:7,13,15,21 222:1,7,8 224:13 228:21 229:3,8 231:12 232:6,10 233:4 241:18 242:7 302:11,13 objectively 10:8 114:11 objectives 220:1 224:19 obliged 340:12 obliterated 127:20 observation 11:6 25:6 40:3 48:4 57:11,22 58:21 59:6 61:11,17 62:8 73:10
--	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 59

116:17 122:9 186:19 212:16 258:1 357:6 observational 19:19 146:5,8 150:16 151:19 observations 142:3 243:18 obstetricians 33:5 obstruction 84:17 obstructive 84:13 86:5 obtain 25:10 34:14 218:5 226:2 298:9 305:19 obtained 33:22 43:12 47:19 298:20 367:22 obviate 267:19 obvious 86:5 288:13 obviously 26:1 49:10 55:2 72:20 96:11 114:22 115:22 142:5 294:13 316:12 318:19,21 332:6 355:10 occur 85:18,19 87:18 107:1 115:19 141:12 153:16 164:20 210:18 237:18,21 238:5 240:17 265:13 302:2 307:12 occurred 41:9 42:19 195:5 201:14 269:21	278:13 300:19 occurrences 34:2 occurring 31:5 141:11 151:2 occurs 49:16,19 207:2 237:5 October 368:4,5 offer 336:20 offered 129:22 144:1 office 2:17 13:2 28:14 33:19 34:1,5 144:12 211:12 356:7 office-based 29:12 33:15 65:9,12 officer 4:8 15:10 official 15:21 off-label 37:19 offspring 140:7,12,16,21 141:6,12,14 off-treatment 236:15 237:8 oftentimes 71:13 226:6 Oh 62:21 185:4 OK 327:4 okay 65:13 73:4,5 74:17 96:8 171:17 173:2 207:16,19 248:16 269:18 279:3 327:6 328:22 331:20 340:7 345:4 347:12	old 58:11 140:9 290:19 314:15 older 31:15 35:18 38:18 43:9 48:18 132:11,14 138:22 141:11 157:1,3 189:20 192:10,12 193:13 204:6,7 283:19 284:18 290:19 302:21 314:13,15 335:4 348:10 359:14 360:2,9,17 oldest 43:8 133:2 156:19 OM 70:19 once-daily 271:9 one-half 45:2 290:18 ones 118:11 158:12 191:16 196:21 202:10,13 252:17 350:15,20 351:4,6 358:14 one's 364:17 one-third 290:18 one-year 18:14 61:20,21,22 62:2 71:11 195:5 ongoing 42:11 149:2 167:4 182:14 185:22 312:12 337:22 onset 294:19 onto 73:18 276:9 on-treatment	236:14 237:9,12,19 open 6:9,19 11:6 18:16 116:17 143:8 186:19 opening 11:4 open-label 16:17 129:20 operated 190:12 191:13 operation 195:13 operational 338:18 opinion 87:13 95:5 100:8 136:20 137:11 181:20 opinions 6:7 opposed 115:9 116:12 opposite 359:18 optimistic 233:22 optimize 17:1 options 289:15,18,19 oral 119:12 order 2:12 12:17 24:20 40:16 95:20 144:15 150:10 192:1 203:10 212:11,20 222:3 225:13 226:11 236:6 285:10 310:5 337:19 339:12 348:6 organ 287:20 organizations
--	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 60

322:7 original 21:9 117:1 182:21 184:6 304:3 originally 129:20 152:21 280:13 orlistat 31:12 32:8 34:11 35:4,12,17,22 36:2,10,18 37:5 38:16 40:4 43:8,21 50:1 136:5,9,13,18 194:19,22 195:1 196:16 197:2 199:7 200:21 202:5,16,21 248:2 249:12 259:12 348:15,17 358:13 osteoarthritis 189:13 osteopathy 33:3 66:3 others 81:7 136:15 143:13 160:14 191:18 192:4 194:8 202:20 312:13 319:1 357:18 360:22 otherwise 319:3 331:13 352:13 370:13 ought 73:14 331:2 ourselves 171:3,4,6 360:8,19 outcome 54:22 106:6,11 108:19	119:10 121:6 147:12,20 151:13 162:17 163:21 168:7 169:20 203:6 204:16 219:12 233:3 234:2 235:18 236:1 241:12,17 275:7 281:4 293:2 336:19 337:20 353:17 355:5 370:13 outcome-driven 211:20 outcomes 12:8 14:5 20:2 49:14 98:12 107:15 118:17 129:14 133:7 137:21 146:20 147:11,21 148:3 183:6 184:4 201:17 203:9 219:22 223:5 226:12 252:3,13 265:20 270:13,18,20 271:2 276:22 280:16 283:14,18,21 288:12,20 289:6 291:19 292:4 293:3,5,6,22 294:8 295:4,6,15 296:6 302:1 304:7 312:3,13 319:10 321:3 325:13 outline 29:4 outlined 27:11 outpatient 29:4,6	30:3,18 32:1 65:12 output 88:6 93:7 outside 116:11 134:9,15 135:3 191:2 368:14 outsider 69:20 outstanding 137:15 outweigh 17:3 21:2 308:20 318:1 336:7 outweighed 271:20 308:4 309:11 outweighs 8:8 overall 31:5 59:22 60:3,17 70:3,4,5,6,10 127:15 132:16 133:1 151:6 188:19 190:8,14 233:10 241:10 242:3 294:8 317:14 318:5 330:21 overcame 123:17 overcome 361:20 overemphasized 111:1 overfeeding 365:11 overlap 63:14 286:12 overlapping 29:18 36:4 41:18 55:17 overly 233:22 overproduced	82:2 overproduction 81:21 overshadow 189:16 oversimplifies 292:10 overt 272:16 273:6 275:15,18 over-the 31:11 overview 12:22 101:12 overviewing 75:6 overweight 11:20 18:1,2 19:14 39:2 70:17 87:11 91:18 142:22 145:9 148:6 156:5,9 207:8 366:20 oxygenation 84:16 <hr/> P <hr/> p.m 186:7 369:6 package 114:22 203:13 packaging 332:22 packet 49:6 page 49:6 50:4 64:5,21 324:15 pages 370:4,6 PAI-1 77:1 paid 32:14,18 43:17,20,21 67:12,16 69:1 painted 252:2 pair 206:5
---	---	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 61

<p>panel 11:8 49:1 54:6 75:2 76:21 103:20 104:9 110:15 116:3,8,19 185:3 186:11,21 187:2 199:17 211:9 270:3 301:8 303:13 304:1,2,4,6,9,16 331:6 340:6 362:7 368:18,20</p> <p>panelists 304:11 327:8</p> <p>paper 82:8 93:19 105:9,10 133:12 143:5 152:13 182:9 184:1,21 185:3,7 188:11 190:20 192:14 199:11 250:16 256:3 263:18</p> <p>papers 76:9</p> <p>paracrine 80:11</p> <p>paradigm 76:2,13 85:16 90:20 93:12 103:18 109:1 114:2 222:10 226:1,6 262:3 362:11</p> <p>parallel 131:14 162:7 287:8 357:20</p> <p>parameter 225:10,12,16,20 226:3 233:19</p> <p>parameters 292:7</p> <p>Parks 2:19 321:9,10 322:20 323:5 324:4</p>	<p>326:3,10 329:18,19 340:14,21,22 355:7,14 361:22</p> <p>partial 176:13,14</p> <p>partially 97:10 326:3</p> <p>participant 10:18 299:13</p> <p>participant/staff 173:19</p> <p>participants 7:20 10:19,22 150:6 151:18 152:1 153:13,14,19,22 154:11,16,21 155:2,5 156:4,19 157:14 167:18,19,22 168:5 169:10,17 173:3,5,18,21,22 174:3,4 176:8 190:19 203:16 204:6 283:19,20 284:3</p> <p>participate 10:13 11:7 116:18 186:20</p> <p>participating 9:20</p> <p>participation 25:17 125:16</p> <p>particle 82:18 83:6 107:8,11</p> <p>particles 80:3 82:1,2,14 83:7,14</p> <p>particular 8:7 9:7 10:2 23:4 24:15 26:1 28:4 38:19 96:19 123:11</p>	<p>137:16 254:20 292:19 305:21</p> <p>particularly 19:15 64:20 76:14 78:13,17 81:22 85:22 97:14 100:22 108:1 114:20 181:11 193:2,9,12 194:3 243:13 279:2 291:10,19 296:4 304:22 364:18 367:18</p> <p>parties 367:16 370:9,12</p> <p>partition 267:14</p> <p>partitioned 207:22</p> <p>partitions 208:22</p> <p>pass 152:2 333:17</p> <p>past 28:9 102:14 298:8 341:2</p> <p>patents 9:3</p> <p>path 82:20</p> <p>pathobiologic 288:14,15,17 289:2</p> <p>pathobiological 288:10</p> <p>pathology 97:11</p> <p>pathophysiologic 181:14 184:14</p> <p>pathophysiological 1 88:8 185:15</p> <p>pathophysiology 13:10 75:7,22 86:8 185:11 290:8 292:11</p> <p>patient 16:19</p>	<p>24:21 29:14 32:6 34:9,18 38:3 41:22 42:2 44:16 46:1 47:20 50:13,22 53:16 73:8 104:15 107:21 114:3,18,20 172:6 183:10,12,13,14 190:12 197:11 212:17,18 214:3 229:20,22 230:1,4,6,12,19 231:1,5,9,11,15, 19,21 232:4,5,7,11,13, 17,20 234:7 251:9 273:19 279:16 287:4 289:21 290:6 314:7 356:5 362:2,10,22</p> <p>patients 11:19,21 16:6,13,16 17:2,7,12 18:4 21:16,19 22:4,19 23:1 26:9 27:6,14 28:5,7,10,12 29:11 31:21 32:2,4 33:22 34:4,14,22 35:2,3,8,14,17,1 9 37:22 38:12 39:2,5,9,14 40:15,18 41:6 44:10,17 45:20 46:22 47:7,12,19 48:10,14 50:11 51:5,8,9,14,19 52:5,6,8 55:1,11,16 62:16</p>
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 62

63:5 64:6,8,17 67:4,8 68:3,22 69:12 70:14 73:3 74:2 80:20 81:17 82:3,21 84:8,14 86:9 87:14 88:6,7 90:16 92:2,9,13 93:13 94:6,15 103:22 106:21 107:2 108:2,3 112:2 113:5,19 119:14 153:7 172:13 200:1,15,17 204:22 205:8 207:8 208:14 209:20 210:5,16,22 212:10 218:19 219:7,9 229:21,22 234:4,5,6 245:19 246:6 267:4,18 273:21 290:19,22 291:17 293:21 295:1 302:17,19 304:21 305:18 311:6 312:15 316:16 317:2 321:21 322:18 334:18 335:1,4,6 338:6 346:10 348:14 349:13 356:6,7,11,16,18 ,19,21 362:19 364:7,10 patient's 33:14 48:5 Patients 27:17 83:8 86:3 90:22 patient-year	355:19 pattern 13:6 58:20 126:12 140:16 161:9 162:1,4 202:8 269:13 341:17 patterns 33:16,19 35:6 66:17,18 132:15 133:1 183:20 Paul 4:7 12:15 86:20 94:8 247:5 pause 76:18 pay 14:3 116:10 payer 40:14 payers 30:10 32:15 paying 13:22 66:19 172:2 payment 29:9 32:10,12 67:18 68:19,22 69:8 payments 69:5 PDAY 89:5 PDDA 33:13,15 peak 31:5 130:18 pediatric 3:11,17 33:10 89:6 pediatrics 3:11 5:5 pedometers 149:21 pelvic 78:12 Pennington 211:2 people 52:9 55:21 56:19 63:20 67:7 68:4 72:8,10 76:10 79:10	83:12 87:9,11,13 89:7 99:11 102:6,9 108:4 114:7,8,13 115:16 117:15 118:2,18 119:6,9,17 120:3,12 121:14,17 122:11,15 123:16 124:10,13 125:3,10 127:14 132:3,11 134:11 136:1,16 137:3,9,18 138:3,4 140:11 148:9 149:3,18,22 150:11 152:3,7 157:16 158:7,10 160:16 161:2,7 164:17 173:8 176:20 183:4 185:20 192:10,18 201:7 203:10,12 205:12 208:5,17 209:12 246:22 247:6 250:4 251:2 257:1,4,7 259:13,18 262:12,13,16,21 263:6,12,19 264:1,14,22 268:9,13 269:3,8,13 278:18,21 279:6 281:15,18 282:10 315:20 316:9,10 318:12,20 319:7,12 321:18 332:22	333:10,20,21 336:3 342:2 343:16 346:1 350:14,18 351:2 363:5,6 364:20 365:14 366:1,11,17 367:4,16,18 people's 129:3 135:17 per 10:12 30:20 46:20 47:4 80:13 85:20 87:8 91:4 93:4 119:6 122:9,10,17,18 135:12,14 149:4,6,21,22 150:3,20 188:19 195:16 217:6,11 218:16,19,20 219:7,9,10 246:5 276:19 303:9 311:4 318:7 percent 17:6,11,13 19:1,16 23:2,3,4,6 24:1,3,10,11,12 27:19 32:16 33:1,4,6,11 34:5,7 38:1,11 40:18 42:15 43:4 44:20 45:4,14,21 47:11,15 50:5,7,14 51:2 52:5 62:22 64:22 65:6 71:11 72:6 74:3 87:9 100:13 101:22 102:2 103:5 105:5 108:4 112:1 120:8 121:1 122:11,18,19
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 63

125:2,21 127:12 130:22 131:9 136:18 140:11 148:8,11,12,17,1 9,20 149:14 150:13,14,20 151:4 152:4 153:12,13,18 154:7,12,16,20 155:1,2,3,5,6,12, 13 156:10 157:14,18,19,20, 21,22 158:1,2,3,8,11,1 9 159:5,6,7,9,20,2 1 161:5,6,15,16 162:12 163:11,13,17 164:22 165:8,9,11,13,14 ,15,16 167:22 171:22 172:1,16,18,21 173:2 175:1,2 179:14,18 180:5,8,9,11,12 188:19 191:5 193:20 194:15,22 195:2,19,21,22 196:21 197:3,7,8 198:18 199:20,22 200:8 201:7 204:15,16,19,21, 22 205:1,6,10,11 206:8 208:10 209:3,4,5 217:4,6,9,11,18, 21 218:1,14 219:5,8 221:8,10,19 222:4 227:2,6,14	228:1,4,9 229:10,12 230:13,14,15 231:3,8,11 232:5,15 235:4,13,14,19 240:15,16 241:5 247:1 261:12,14 263:8,10 267:15 271:10 273:12,16,22 274:1,2,19 275:20 276:14 278:7 279:9,10,14 280:2,5,18,19,20 ,22 284:4,11 285:1,7 307:5,9,14,20,22 308:7,9,13,16,18 309:17,21 310:14,19 311:4 318:7 328:17 330:15 333:15 335:2 338:22 339:7 348:17,18,20 350:19 356:14,16 358:15,16,18,20 359:19 366:16,18 367:1,2 percentage 54:2 64:11 160:21 161:3 356:14 percentages 167:18 356:3 percentile 209:2,3,4,7 percentiles 209:1	perception 364:17 perfect 103:2 perform 312:8 performance 305:13 performed 38:8 156:14 194:18 234:17 perhaps 12:9 53:20 90:3 103:7 106:12 135:19 294:13 314:16 338:19 341:1 362:21 period 31:6,18 32:13,19 38:15 40:3 42:1,3,22 48:4 57:4 111:1,2,11 112:3 120:19 121:4 132:4 135:7 137:1 203:15 234:4 258:1,19 259:8,14,18 260:1,4 265:1,6,13,17 304:12,13 366:6 368:22 periods 67:5 210:8 265:5 335:14 peripheral 87:21 88:1,2 147:19 273:1 288:4 permanent 102:7 103:1 permanently 332:12 permission 192:16 permit 78:2	perpetuating 142:13 persistent 44:18 45:3 111:16 person 4:13 128:4 146:9 175:12 343:17,20 365:8 366:8 367:10 personal 10:18 186:8 365:9 personally 265:10 266:22 personnel 134:6 persons 118:12 145:9 290:16 person's 344:12 perspective 42:21 53:5,22 54:14 70:11 251:1 261:16,17 316:8 pessimistic 144:3 Peter 15:1 ph 92:4 Pharma 40:11 pharmaceutical 114:4,21 357:10 pharmaceuticals 110:3 pharmacies 30:7,15,22 40:15 47:7,8,14 66:18 pharmacoepidemi ologist 5:5 pharmacokinetic 22:3 pharmacokinetics 22:1
--	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 64

pharmacological 113:14 207:5 pharmacy 32:1 41:8 42:2,14 43:17 47:10,12,15 phase 16:5,13 18:12 21:22 22:10,17 23:10 25:12 26:19,21 27:10 28:2,9 83:20 115:21 120:6 129:17,20 271:4 278:22 283:16,19,22 284:2,5,16 285:6 297:6,19,22 298:7,16 299:19 303:16 305:10,12 312:2,9,11 314:5,10 319:8 phases 21:21 phendimetrazine 31:16 phentermine 31:6,19 32:5,8 34:11 35:4,6,10,18,20 36:2,10,18 37:5 38:14,18,19 40:3,8 43:20 48:12 53:10,12,16,21 69:4,7 114:6 197:20 198:10 205:19 206:6,13 259:7 348:15,17,19 349:4 Philadelphia	28:21 phlebothrombosis 86:10 Phoenix 117:7,8 phones 2:4 PhRMA 355:15 physical 91:18 119:17 120:11 146:20 149:11,19 157:6 158:21 159:8 172:17 178:1,14,17,18 350:21 351:3 physically 181:9 physician 33:9,12 34:21 53:22 65:10 113:20 150:6 197:11 289:21 343:20 344:19 345:3 physicians 29:12 53:12,15 66:1 75:3 90:1 183:12 210:15 344:11 physician's 66:6,11 Physicians 53:8 202:8 physiological 93:12 physiologist 185:10 PI 263:7 picked 44:15 188:9 198:1 203:12 picking 72:18	136:1,2 Pickwickian 86:7 picture 70:6 100:11 252:2 335:19 pill 172:8 Pima 117:14 138:18 139:9 pin 332:15 365:7 pioglitazone 263:17 pivotal 294:18 PK 22:4 placebo 17:11 20:14 23:1,5 24:9,14 25:22 26:22 27:15 57:13 119:20 120:1,17,21 121:9 122:10,12 123:12 125:9,19 126:6,10,15 127:9,21 129:17,21 130:14 131:16 132:19 134:4,12 135:3 136:8,12,19 195:6,7,9,10 196:15,21 203:18 204:5 210:10,12 222:17 235:16 247:8,10 249:17 250:13,18,21 251:2,7 259:9 264:22 265:15 271:9 272:4 274:16 276:17 277:1 278:10	280:18 281:5 283:3 297:7,9,15,17 298:3 303:1,2 319:14,21 322:3,4,21 323:3,15,17 324:17 353:21 354:18 358:20,21 359:1 placebo- controlled 16:14 18:15 22:18 23:11 206:18 265:18 272:2 284:7 306:4 321:7 322:14 323:11 placebos 250:19,21 placebo- subtracted 196:5 197:9,13,16,18 247:14 250:17 276:13 placebo-treated 17:14 24:4 placed 82:8 places 187:7 placing 149:16 plan 27:13 234:20 246:15 274:11 planned 12:2 129:10,15 218:9,13,21 219:1,4,10 230:8,20 231:15 241:7 246:2 312:2,21 320:10
---	---	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 65

plans 13:12 30:11 34:20 312:5,16 313:2	147:17 149:8 176:14 180:19 196:16 213:11,14,21 214:1,6 234:16 237:8 248:2 251:7 253:9 263:8 277:18 278:5 281:12,14 282:13 283:1 313:9 348:19	329:4,8,11,14 330:5,13,15,20 331:6,7 332:14 338:16,19 339:1,8,11,16 340:1 341:15 345:16 351:12 364:4,5,8,13 365:17,20	237:6,10,14,17,2 0 238:1,8,10 242:18 248:22 274:4 280:17 282:6,9 283:8 285:9 287:11 295:15 297:10 300:18 302:19 318:17 334:16 336:16 350:7,8 356:5 357:2 359:12,13,16,19 360:3,4,9,11,16, 17 361:2,4,10,14,16 ,18,19 362:2,14,17,22 363:10
plasma 118:21,22 119:11 292:5		pointed 83:9 146:15 150:22 154:3 328:15 350:12	
plateau 111:12 115:16		points 13:1 30:13 153:11 164:10 232:22 241:15 278:2 285:8 302:10 325:11	
plateaued 130:19 206:7	pm 1:11	Poirer's 94:8	populations 63:14 109:19 117:9 141:10 142:18 226:10 234:8 236:21 238:3 242:20 284:17 318:9,11 334:13 362:10
plateauing 154:11	podium 28:18	Poirier 86:20	
play 81:12 224:18 241:19 309:16 316:14 325:1 357:11	point 14:7 26:9 43:19 45:2 52:4 61:19 67:15 85:7 88:10 89:4 96:9 99:17 100:8 106:9 108:6 112:15 115:17 121:5 122:3 153:6 164:18 168:21 173:7 177:19 186:1 195:5 216:16 217:12 220:18 222:2 240:2 244:16,22 245:6 249:14 252:11 262:11 269:20 270:11 271:1 275:19 278:14,20 280:19 281:2,12 282:17,20 283:5,7,12 288:21 300:21 306:14 308:9 309:10 311:9 316:13 317:6 327:4,10,21 328:3,6,7,9,19	police 263:12	
player 95:2 98:16 114:21 193:4		policies 359:10	
players 95:4		pool 312:11	
playing 316:21		pooled 188:13 191:13	
plays 81:2 87:7		poor 240:12	portion 233:1
playwrights 143:22		poorly 106:18 159:12,13 192:3	pose 20:20
please 2:3,7,13 7:2 49:1 51:1 71:18 116:4 186:8,11 270:3 325:22		population 11:21 16:19 30:21 31:1 54:3 70:17,18 99:18 123:6,10,18 139:11 141:16 142:16 150:19 160:1 176:15 216:12 225:10,12,16,20 226:3 235:7 236:22	position 20:17 264:17 360:8
pleasure 15:12 187:2			positive 60:2 72:1 146:4 162:18 364:6 365:6
plenty 54:7			possibilities 67:3
plot 44:17			possibility 151:15 239:20 258:18 296:10 344:4
plots 204:13			possible 143:19 167:18 247:17 257:10 300:15
plotted 46:14 217:15 227:16,18 247:21			
plug 273:17			
Plugging 227:7			
plus 41:14 85:18			

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 66

301:4 330:12 possibly 324:8 post 9:5 21:7 36:15 239:9 300:14 308:12 post-approval 239:22 240:4 241:2 302:3 304:13 310:13 311:13 334:14 post-baseline 25:4 post-marketing 239:9,14 240:19,20 299:11 308:21 postprandial 82:19 post- randomization 342:17 postulated 275:2 potential 8:6,8,13,18 12:7 92:18 103:15 106:8 208:18 210:19 214:7,8,12 219:22 220:1 236:21 296:8 299:11 308:4 320:14 342:15 potentially 56:2 66:21 97:1 359:12 360:1 361:11 potentials 92:19 pound 102:22 113:9 pounds 52:11,12	power 23:3 150:14 212:20 223:12,17,20 224:2 226:1,5,11 227:6,13 228:8 229:14 230:15 239:17,18 261:21 273:11 279:9 281:22 309:21 333:6,8,16,18 339:6,7 powered 236:8 239:3 240:5 241:13 244:14 279:11 284:10 299:7 315:12 powerful 98:6 117:17 powering 224:11 234:1 241:16 practical 334:9 354:22 360:1 practice 5:20 33:3,20 65:8 66:2 113:5 183:20 184:6 252:21 323:1 practices 33:17 34:22 practitioner 65:21 practitioners 33:9 66:6 pramlintide 198:4 206:6 pre 139:17 214:3 299:11 334:18 335:1 362:19 pre-approval 9:5 61:4 239:8,13,21	240:3,17 241:1 271:4 283:22 302:3 304:12 309:18 334:13 335:18 366:4 preceded 139:15 precisely 257:5 pre-define 213:1 pre-defined 214:11 pre-diabetic 139:16 140:2,12 141:5 predicated 339:14 predict 185:20 201:1 210:8 295:3 predictable 338:21 predicted 97:3 122:14 predicting 268:16 predictive 141:22 predictor 98:7,11,21 105:19 106:2 159:10 predictors 91:19 98:22 138:16 160:1 167:8 predicts 200:19 350:6 predispose 106:22 predisposed 304:22 predominant 288:15,16 349:5 predominantly	43:17 89:14 141:13 286:22 predominates 289:2 preempting 334:21 prefer 195:20 265:14 preference 244:5 261:19 preferred 130:2 pregnancies 141:6,13 pregnancy 68:12 69:10 139:14,15,21 141:14 142:12 pregnant 66:22 68:6,9,16 139:13 141:18 142:11,13 premature 24:21 129:9 prematurely 25:11 280:6 pre-menopausally 78:13 preplanned 315:11,17 pre- randomization 195:5 prescribe 348:4 prescribed 11:22 16:7 31:17 38:21 56:1 66:7 348:2 prescriber 29:9 32:10,22
--	---	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 67

prescribers 33:2,7,15	49:5 57:10 116:15 144:7 167:13 168:10 176:19 177:5,10,13,14,1 5 179:12 211:7,18 213:15 225:3 233:1,20 239:11 243:4,7,12 270:9 303:12 315:20,21 334:12 349:1	19:10 54:20 59:19 61:1 88:4 91:6 93:8 97:4 103:7 106:6,11 145:20 148:10 161:22 162:3 165:18,19,20,21 166:1,16 167:11 179:22 184:11,18 191:19 202:19 209:19 256:12 258:6 271:14 276:18 278:8 279:3 324:17 325:18 345:22 346:14 363:8 367:5,7	prevalent 274:4 287:6,16 293:1 prevent 132:2 135:8 137:16 141:18 150:10 prevented 118:10 preventing 126:21 137:22 138:2 257:15 prevention 75:13 85:8 118:7 127:1 128:10 135:19 136:1 153:17 154:6 169:9 195:15 207:12 263:18 previous 28:12 43:3 45:11 60:19 83:10 93:4 113:12,19 205:5 218:3 219:11 227:13 229:14 237:10 294:10 307:17 311:2 previously 15:4 33:8 127:11 227:8 230:11 primarily 26:10 145:10 150:3 159:2 166:11,18 primary 9:3 24:16 25:2 33:2,7 38:22 59:4,14 60:13,21 65:1,6,20 66:1,4 74:9 118:11 119:10 121:6 147:5 152:20,21,22 153:4 182:21 204:16 213:1,18
prescribing 33:19 49:19 55:21 66:17 210:15			
prescription 29:6,9 30:4,9,14,16,19 31:14,22 32:3,5,10 34:3,15,19 35:1,9,10,15,20 36:5,14,16,18 37:5,22 40:2,13 41:10,20 42:8 46:20,22 47:4 48:20 67:10 70:15,19 71:2,4 172:20 348:8,13,15	presentations 13:9,17 169:8 186:17 211:8 255:4 340:20 368:18		
prescriptions 29:19 30:7,20,22 31:4,8 32:12,13,18,21 33:1,11 38:11 41:16,18 47:6,8 64:22 67:12,15 348:20 349:2	presented 29:15,20 50:5 219:15 223:19 236:18 253:21 293:16 301:6 307:17	pressures 86:13 87:12	
presence 48:5 81:19 83:22	presenters 368:17	presumably 49:11 53:19 78:16 94:14 97:9 106:17 250:4 366:1	
present 2:3,7 29:2,6,22 39:22 40:6 95:11 211:13 215:6 219:13 235:8 249:9 252:12,13 290:14	presenting 75:4 116:21,22 260:17 286:13	presumed 329:7	
presentation 10:9 12:20 14:10 15:8 29:5 30:2 32:6 39:18 43:4 48:21	preserve 212:20 218:11 238:4 242:13,20 246:9 303:6	presumption 74:13 360:22 361:21	
	preserved 242:16	pre-trial 297:13	
	preserving 252:5,6	pretty 71:9 96:1 162:20 204:2 265:8 316:20 320:19 340:5 342:21 360:3	
	prespecified 13:20 212:13 234:20 238:3 273:3 303:8 305:13	prevalence 21:17 30:20 39:17 90:15 92:20 142:15 161:13 164:13 287:8,9 289:8 290:15	
	press 2:6		
	pressure 12:7 17:9		

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 68

235:7 242:20 270:12 272:5 277:2 279:18 280:14,16 281:4 298:9 302:11,16 304:20 313:10 318:11 principal 12:11 prior 36:13 148:21 152:2 233:17 296:22 298:10 300:22 306:1 310:6 332:7 private 5:19 65:7 pro 80:17 81:10 82:1 84:8 PROactive 323:10 probability 215:9,13 223:17 224:4 240:15 307:13 probably 13:21 14:3 48:5 54:9 56:17 70:3,9,21 74:14 77:9 80:9,16 81:1,3,6,12 90:14 92:11 95:6 151:20 180:3 205:2 208:7 209:7 244:19 256:11 260:6,11,13 334:5,7 337:5 340:15 355:20,21 356:22 357:8 363:16 problem 72:20,22 73:1 99:12,13 102:8 106:19	136:14 137:7 139:5 141:13 142:21 174:14 178:18 252:4 316:11 352:1 problematic 61:13 problems 139:2 169:3 172:9 189:12 260:2 procedure 200:18 333:4,19 334:2 procedures 283:2 proceed 11:3 116:14 186:16 proceeded 71:15 153:3 proceedings 6:21 370:7 process 15:19 225:19 295:9 363:1 produce 146:19 164:22 167:4,10 207:10,11 produced 77:13 159:18,21 166:14 201:20 206:6 256:19 258:5 produces 180:15,18 producing 203:8 product 21:6 22:13 24:2 29:10 35:10,15 36:19 38:16 222:15 239:8 293:14 298:16 309:2 330:21 349:5	production 77:1,2,3,6 80:3,21 81:18 82:13 83:10 productive 6:14 products 10:17 15:13 19:6 29:4,7,13 31:8,14 32:7 34:10 35:7,12,13,16 36:21 37:7,14,17 38:6 158:20 211:16 238:12 321:16 338:10 product's 309:3 Products 11:13 15:11 285:18 professor 3:7,10,13,20 4:9,17 5:1,5,10,13,17 profile 22:3 205:16 209:17 222:18 302:21 317:14 321:15 330:21 341:8 profiles 22:2 prognostic 109:14 program 3:18 27:13 28:2,4 51:6 111:16 118:7 120:13 125:16 127:2 133:21 145:8 146:18 149:8,11 153:17 154:6 156:15 158:14 159:3 167:8 169:9 176:22	195:15 207:13 209:9,12 257:8 284:3 296:13,21 299:19 301:21 310:6 315:9 335:10,11 341:4,10,11,13 356:5,9,18 368:8 programs 21:18 22:18 27:11 28:9 51:7 59:12,17 60:8 67:7 173:6 299:15,19,21 300:9,20,22 301:19 310:12,21 311:19 312:1 313:14,22 314:3,19 315:2 321:2 336:14 337:16 356:22 progress 118:16 progression 53:1 96:3 294:20 progressive 53:2 115:8 290:9 pro-inflammatory 77:3 80:5,15 projected 30:5 33:18 40:17 proliferation 100:6 prolonged 86:18 promising 23:13 promote 150:3 proper 72:7 139:18 properly 258:20 properties
---	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 69

333:4,5,14 334:2 prophecy 267:7 proportion 11:19 17:12 23:22 24:3,18 32:17,21 35:8,11,13,14,16 ,19 38:17,20 44:10,17 46:3,10,12 48:17 57:21 69:5 287:11,12 314:14,17,20 348:9,14,22 proportional 234:17 proportionally 43:21 proportions 32:11 proposals 235:22 312:18,21 propose 187:14 312:8,11 proposed 264:16 267:17 306:3 312:14 320:22 proposing 264:11 Proschan 5:7 50:3,4,17,20 105:16,17 174:11,12 246:18,19 248:14 249:4,14,22 250:3 251:13,15 252:10 258:14 260:20 327:5 332:20,21 prospective 188:10 299:10	300:9 prospectively 270:1 294:18 299:4 305:8,15 312:2 313:4 315:10 prospectively- planned 312:8 protein 83:4 protocol 114:10 246:5 279:19 303:9 306:2 prove 332:2 339:21 proved 340:3 proven 112:14 349:15 provide 12:21 13:3 15:12 19:5 32:6 34:9 39:19 169:10,12 221:6 226:21 295:9 303:21 306:2 317:21 341:5 provided 7:20 10:6 33:13 34:2 217:16 218:7 307:19 308:20 309:5,11 provider 67:6 69:15 providers 38:22 65:1,6,20 66:5 67:6,9,17 provides 23:2 30:6 33:16 216:5 229:6 232:13 234:4 311:20 providing 67:18	133:17,22 286:4 Prozac 206:19 psychiatric 274:8 psychosocial 148:2 public 7:21 9:16 10:7 11:5,6 31:10 70:11 116:16,17 186:18,19,20 287:18 290:22 publications 251:3 publicized 296:13 publish 133:12 published 12:2 17:22 28:4 79:22 105:9 117:10 128:17,18 130:12 138:14 139:8 153:9 190:15 192:14 193:18 194:19 199:9 201:13 207:18,19 263:19 304:18 publishing 167:21 pulled 327:13 pulmonary 86:3,11,13,14 93:7 201:21 pulse 98:10 106:5,10 109:5,7,10 202:19 278:8 279:3 pure 269:11 purpose 19:5 69:22 208:12 286:11 307:18	308:12 purposes 8:21 puts 292:8 putting 171:14 360:8 puzzled 320:4 <hr/> Q <hr/> QRS 92:6 QT 94:9 QTc 86:18 92:7 93:11 QTcs 94:10 quality 135:12,14 148:2 quantify 173:16 quantifying 306:6 quarter 44:22 45:12,13,19 48:10,13 quartile 44:5,13 question 41:9 42:3 49:4 55:5,18,19 56:6 57:9 59:8 63:16 64:3,13,19 66:13 67:12,21 68:10,19 69:14,19 70:3,12 87:21 95:22 98:12,14 102:14 103:19 104:20 105:18 106:5 107:10 110:2,19,20 111:13,14 113:3,18 115:2 117:22 124:17 125:22 129:2 143:8 168:15
--	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 70

171:9,20 176:10 178:22 179:9 180:15 181:13,16 184:8 185:1 225:4 235:6 242:7,18 244:4,12,20 246:3 251:14 253:5 255:2,5,18 256:15 258:10,22 260:20 261:5 262:9 264:6,9 267:2 303:14 304:3,4 316:5 317:9 318:14 319:13,18 324:11 329:10 334:20 338:14,20 339:3 342:9,11 347:6,20 352:18 353:7 355:1,8 357:3 359:22 360:12 362:20 366:15 368:13 questions 12:5 48:22 51:16 54:7,8 74:1,19 95:15,19 99:4 101:21 110:14,17 138:13 168:11 170:3 174:7 175:9 176:18 186:2,4,5 211:4,8 238:9 243:1,8 245:11 246:19 251:16 260:12,14 269:19 315:22 316:2 325:14 336:9 340:18,19	341:22 342:2 346:21 352:15 363:17,19 368:16,19 question's 54:11 quick 170:3 173:9 176:18 185:1 267:2 quickly 179:11 271:1,5 280:1 283:12 365:13 quite 6:7 28:12 69:2 75:5 100:14,19 113:8 122:14 156:1,15 158:21 162:11 176:21 191:16 195:22 206:7 231:19 240:12 269:1 274:4 284:21 356:4 357:22 365:21 quotes 300:8 <hr/> R <hr/> rabbit 114:16 race 23:8 race/ethnicity 156:18 racial 21:17 28:8 167:5 raise 49:1 86:13 95:20 345:10 362:6 raised 12:5 317:17 362:20 raises 74:1 345:7 raising 366:15 random 253:22	331:13 randomization 62:3 130:11 132:11,14 238:4 242:20 246:9 252:5,7 259:9,22 278:22 310:2 367:21,22 randomize 175:21 176:3 259:3 269:8 366:1 randomized 23:2,11 27:14,15 51:10 62:17,18 118:8 119:15,19 145:5 146:1,3,11,12 147:2 153:13 190:10 199:12 203:17 204:3 206:18 223:22 235:16 258:20,21 259:21 265:18 269:15 272:2 277:1 278:10 282:11 284:7 294:19 297:7,12,20 322:19 342:18 range 22:4,6 28:10 59:5 96:2 135:16 198:5 199:15 208:10 330:11 ranged 43:7 45:7 121:4 ranges 235:14 ranging 297:8 rapid 115:9 rapidly 83:14	150:11 204:9 293:21 rapport 169:21 rarely 99:7 359:4 Rasmussen 5:21 9:20 10:2 63:10,11 174:6,9 334:10,11,21 335:15 347:4,5 Rasmussen's 9:22 rate 52:21 59:20 61:14,15 72:5 88:5,11 92:6 93:10,11 94:9 98:2,6,10,17,19, 20 105:19,22 106:7 109:8,9,18,22 110:1,3,10,11 113:14 121:19 122:10,17,19 123:22 125:8,10,21 126:13 131:15 147:7 150:17,18 151:4,5,6,8,15 170:14,17,18 171:9 174:14,19,22 176:11,12 191:6 205:10 212:19 213:22 214:1 215:19,20 216:10,12,17,22 217:2,3,8,17,20, 22 218:4,8,9,14,17, 22 219:1,5,7 223:13 224:3,8 227:7,14 228:9 230:5,8,16 231:2,7,11
--	--	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 71

232:2,5,16,19 235:15 242:11,12,13,15 244:10,11 261:3 263:8 273:16 276:19 279:14,18,22 284:22 285:3,5 300:17 306:11,12,13 311:5 318:7 319:2 324:16 337:4,11 351:9 rate-limiting 82:16 rates 24:20 30:20 36:17,21 37:2,4,7,9 39:3,7 115:5 117:13 121:10 122:5,7 123:8,13 131:14 150:20 153:16 176:16 190:2 214:8 215:7 220:10 224:6 230:13,20 231:6,16,22 232:14 235:10 236:16 244:1 275:5 316:13 336:12 346:5,6,8 360:3,5 rather 72:6 82:10 181:20 206:3 212:5 224:17 262:5 263:3 ratio 215:15,17,18 235:1 273:12 274:18 275:19 276:3 279:10 280:20 281:12 282:8,17 283:1,4	284:12 306:13,14 307:6,9 313:19 333:5,7,14,17 rationale 144:22 181:14 RD 215:10 reach 149:22 183:5 195:11 293:21 reached 112:16 218:8 reaching 80:15 reactions 150:11 274:9 reaffirms 304:19 real 24:17 63:19 99:5 179:11 199:2 240:7 246:17 249:16 262:15 264:15 347:22 realistic 21:4 48:1 reality 290:3 360:4 real-life 63:15,17 really 49:20 50:21 51:3 57:13,14 59:17 60:12 61:16 70:7 74:10 79:19 87:6,14 97:5,11 105:19 106:9 108:13,21 113:21 117:22 122:20 123:17 124:9,11 125:15 134:20 139:1,5 141:16 143:22 144:19 146:12 152:12 168:1	171:20 172:13 173:3,21 177:20 178:7 182:19 244:21 245:17,22 246:9,10 247:4,7 250:12 254:9,14 255:3 257:4,18 264:12,18 268:2 269:6 270:14 274:14 275:9 276:2,5 278:12,14,15 317:11 319:16 322:17 324:12 326:16 328:16 331:2 332:15 335:16 345:22 349:15,19 352:9,21 354:2 356:4 359:12 362:5 363:18 364:15 367:16 368:1 real-world 13:6 21:4 269:14 reason 78:17 79:16 83:1 121:12 138:19 173:17 181:16 183:11 268:19 338:17 348:3 358:19 364:11 reasonable 251:11 360:17 361:2 reasonably 259:1 reasons 12:11 97:6 235:21 272:12 310:15 reassurance 309:2 332:14 339:14	reassured 331:1 reassuring 308:10 309:10 320:3 327:5,6 328:7,9 330:14 338:16,18 339:16 342:6 recall 176:19 197:4 223:5 224:14 229:20 259:5 267:16 282:22 recalled 299:17 recap 296:3 received 25:3 30:10 32:2,4 38:13 119:22 127:9 272:3,4 278:4 324:14 347:21 receives 10:12 receiving 31:21 62:16 63:5 114:4 120:20 123:12 recent 72:2 81:20 82:8 90:13 93:19 143:5 235:12,22 recently 103:15,21 127:5 133:12 285:2,6 296:13 362:18 364:12 366:11 receptor 26:12 271:6 recess 116:13 186:15 270:7 recidivism 70:9 recognize 49:1 95:20 294:6
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 72

<p>341:2</p> <p>recognized 6:13</p> <p>recognizes 304:21</p> <p>recollecting 187:4</p> <p>recollection 317:20</p> <p>recommend 111:3 149:14 206:2</p> <p>recommendation 21:10 22:22 122:3 206:17 251:20 304:17 320:9 322:8 326:6</p> <p>recommendations 16:12 19:5 56:20 58:15 304:14 311:17 325:7 329:5 350:1</p> <p>recommended 16:16,20 122:2 145:14 271:19 298:13 299:20,22</p> <p>recommending 115:6 304:7 321:6</p> <p>recommends 305:6,11,18,21 306:7</p> <p>reconcile 261:15</p> <p>reconvene 186:7</p> <p>reconvened 18:9</p> <p>record 6:12 10:21 14:22 28:19 39:15 144:9 370:7</p> <p>recorded 370:4</p>	<p>recruited 338:6</p> <p>recruiting 314:12</p> <p>recurring 295:17</p> <p>red 153:22 189:21 237:4 248:5 306:20</p> <p>redepositing 77:15</p> <p>redraw 134:22</p> <p>reduce 19:20 124:13 125:13 143:4,6,14 147:6 179:8 181:5,7 193:6 195:21 200:3 257:2 275:5 288:19 294:19</p> <p>reduced 19:9 54:12 83:9 89:17 93:16,19,20 97:5 98:22 104:17 112:5 122:17 190:19 191:1 200:7,9 256:19 370:5</p> <p>reduces 187:17</p> <p>reducing 96:15</p> <p>reduction 17:7 19:8 44:14 71:1 80:21 81:3 93:5 94:13 97:5 102:2,10,15,19 103:6 104:22 105:1,4 112:6,10 114:4 115:18,22 120:11 122:18 123:22 124:14,16 125:14,17,21,22 150:14 165:14 177:22</p>	<p>178:1,3,10 190:8,14,17 192:1 193:9 195:19 197:12 224:11 228:2 229:9,12 232:15 233:6 249:1,15 255:8,11 273:12 279:10 293:13,19 295:6 304:20 336:5 353:20</p> <p>reductions 81:1 82:22 83:1 93:7,8 94:9 200:5 241:21 253:11 255:16 265:12 278:11 284:11 344:7</p> <p>Redux 358:15</p> <p>reevaluating 59:1</p> <p>refer 54:12 213:13 220:15,22 272:9 277:5</p> <p>reference 185:6</p> <p>references 140:15</p> <p>referred 207:11 213:7</p> <p>referring 286:2</p> <p>refine 18:10</p> <p>reflect 33:19 360:16</p> <p>reflected 314:13 336:11</p> <p>reflection 100:20</p> <p>reflective 24:16</p> <p>reflects 110:5 364:8</p>	<p>refrain 6:22 7:3</p> <p>regain 120:15 130:19 154:9,11 157:17 158:22 179:14 180:1,2 185:12,21 204:5,9</p> <p>regained 20:11 130:19 132:22 158:4,15 206:22</p> <p>regaining 130:21 137:4 351:4</p> <p>regard 10:4 69:14 302:9 307:1</p> <p>regarding 12:6 19:6 347:21</p> <p>regardless 20:14 129:22 173:20 237:18 258:5 279:1 282:11 327:9 330:10</p> <p>regards 68:8 98:8 233:1 291:5 311:20 314:11</p> <p>regions 323:2,13,14</p> <p>regressing 72:21</p> <p>regression 249:15,18 250:1</p> <p>regular 7:12 8:5,12 42:2</p> <p>regularly 115:2</p> <p>regulate 344:18</p> <p>regulated 9:22</p> <p>regulation 15:18 77:8 91:4 351:19</p> <p>regulations 7:14</p> <p>regulatory 261:16</p>
--	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 73

274:5 296:16 307:18 reject 307:12 rejecting 223:18 224:4 307:14 relate 85:6 90:6 94:13,19 95:11 97:14 106:9,20 107:15 related 8:16 19:21 20:1 57:10 76:6 79:20 81:21 84:22 91:16 106:6,11 139:2 143:1 157:3 160:1 168:20 178:11 181:10 189:11 190:4 191:10,20 192:3 197:8 202:22 257:12 264:10 266:9 365:3 370:8 relates 75:16 82:20 83:15 84:6,12 85:21 87:22 100:10 101:8 102:6 103:3 106:17 324:12 358:3 relating 76:10 90:18 174:7 relation 164:20 203:1 241:6 relationship 22:7 55:7,8 75:9 78:20,22 79:11 83:20 84:2 91:11 101:12 109:17 117:18 165:17,22	166:4,7 168:19 180:2 190:3 208:8 228:7 230:18 231:13 338:21 339:6 352:22 relationships 11:1 92:12 relative 108:19 141:20,21 162:19 189:21 215:12 216:9,13,19,20 217:2,5,9,15,21 218:2,5,11,17 219:15 220:8,9,12 221:2,4 223:13 225:6,7,9,17 226:13,15,20 227:1,3,10,15,18 ,19,22 228:1,3,4,6,10,1 5,17,19,22 229:1,4,7,9,12 230:18,22 231:6,8,10,14,17 ,18 232:1,3,9,11,15, 18 233:7,14 239:22 240:5,6,10,14,19 241:22 242:9 243:22 244:2 245:11 261:4 287:16 307:4,8,20 308:7,9,16 309:17,21 310:2,7,14,18 313:1 324:17 333:14 353:16 354:16 367:8	370:11 relatively 98:13 110:11 297:11 313:18 349:22 relay 330:17 relevant 47:18 216:5 286:14 334:1 reliable 226:2 233:16 reliably 292:5 295:3 relies 223:1 reluctant 331:8 remain 235:6 236:12 remained 122:12 130:14 139:17 140:5,16 194:6 280:9 remaining 316:2 remains 23:17 213:4 225:4 239:19 242:7,18 remarkable 131:7,22 349:19 remarkably 69:21 120:18 130:14 131:3 remarks 11:4 241:9 remember 116:4,10 125:9 186:11 265:2 270:3 281:10 319:20 331:14 341:9,12 368:21 remind 2:3 10:15	11:5 54:5 79:2 93:15 110:15 116:15 186:18 368:20 reminded 7:2 reminder 6:11 116:8 reminds 143:21 remnant 82:1 removal 82:4 removed 17:18 Rena 144:14 176:19 178:9 192:8 363:22 365:8 367:13 renal 90:22 91:2 188:22 272:22 305:22 314:20 356:7,11,16 Rena's 177:12,14 repackage 334:3 repaglinide 40:8 46:22 repeated 58:19 86:12 repercussions 287:18 rephrase 334:20 replace 200:14 replacement 158:20 350:21 replacements 149:17 report 58:15,16 104:9 133:10 157:6,7 158:20 260:22 335:22
---	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 74

reported 9:10 29:12 34:7 127:11 129:7 138:9 263:16	26:12,14 39:16 151:22 293:21 302:4 303:17 311:1,13 315:17 325:12	174:17 323:8	43:1,10 44:7 120:5 121:22 122:2 133:11 137:14 145:1,3 151:10 153:5,9 167:21 181:22 214:9,21,22 215:2 227:8,21 228:13 231:4,20 234:12 235:12 241:1 255:16 270:12 274:13 277:22 278:18 281:8 292:4 294:21 299:8 312:11,12 352:3 364:15
Reporter 370:1,3,19	requirement 239:9,14 299:3 301:17 303:20 311:11 313:21 320:13	respectively 284:11 respond 71:8 114:9,13 201:8,9 208:14,18 209:13 210:5 266:3,11 269:16	resume 116:7 270:6 369:4
reports 33:13	requirements 296:16 308:11 312:5 313:17	responded 53:12 203:20 256:2	resumption 68:15
represent 10:1 310:18	Requiring 310:7,19	responder 269:8 350:7,8	resuscitated 277:5,6
representation 91:5	rescue 321:7	responders 24:19 351:10	resuscitation 204:18
representative 3:19 5:22 7:10 9:19,21 21:15,19 28:2 300:13	research 1:5 4:11,18 47:11 112:4 121:18 134:1 211:2	responding 210:16 262:13 267:18 269:9	retail 30:3,7,15,22 32:1 43:17
represented 31:4 32:20 223:7 310:10	reserve 340:7	responds 184:16	retain 167:18
representing 77:2	residual 308:3,19	response 23:16 105:18 114:15 202:19 210:13 258:17 266:1 268:20 365:22	retained 357:6,12
represents 30:16 40:14 221:18 315:15	resistance 76:1,3,13 79:4,8 80:6,9 81:4,7,10,14,17 82:3,10,22 83:16,21 84:11,15 87:15 88:1 90:20 94:22 99:6,7,12,17,20, 22 103:11 108:22 266:7,9,12,16	responses 203:17	retaining 173:18
reproductive 64:9 68:14	resistant 87:10	responsive 184:14	retake 68:5
reproductive-age 66:22 68:3	resonate 328:22	restricted 279:20 282:15	retention 72:8 90:22 150:3 168:22 169:3,4 173:11,14 174:22 175:1,3 358:4
request 11:8 51:7 116:19 186:21 203:6	resources 335:10	restricting 181:8	re-think 61:7
requested 274:6	respect 9:18 20:16 51:21 70:9 71:22	restriction 181:3	retinopathy 138:4,10
requests 114:18		result 86:14 122:20 214:16 226:17 230:1 287:1 292:13	
require 41:7 139:12 224:8,20,22 234:7 308:21 309:3 311:5 335:1 358:20		resulted 127:17 343:4	
required 22:19		resulting 41:2 227:17	
		results 24:18 25:9	

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 75

retrospectively 300:12	284:17	189:2,21 191:4	240:3,4,5,6,11,1
return 13:17 160:8	Rimonabant-	195:19,22	4,17,20
169:19 211:1	induced 271:11	197:12 203:12	241:2,6,18,19,22
263:8	rise 142:5 258:8	204:8 205:22	242:2,3,4,6,7,8,9
reuptake 276:11	287:7,9	209:17 213:3	,10,14,16
revascularization	risk 11:17 12:1	214:4,10,14	243:15,22
283:2	13:20 17:2	215:8,11,12,15	244:2,9
revascularizations	18:5,21 19:18	216:6,8,14,16,19	245:5,7,11 248:4
213:13	20:20 26:1 49:13	,20,21	251:12 254:3,6,8
revealing 171:4	51:22 52:7 59:22	217:1,2,5,6,9,10,	256:17,19 260:3
reversed 258:2	60:3,4 64:11,15	15,22	261:7,10,13
review 78:2 80:1	68:11 76:5 77:18	218:2,5,11,12,15	262:5,14
92:10 99:4	78:1,14,18 79:19	,17	264:19,20
250:16 251:4	80:19 81:15	219:2,3,6,17,19	265:12,16
320:10,17 324:5	83:17 84:20,21	220:1,3,5,8,9,12,	267:20,21 268:7
328:10	87:7,15 88:12	14,16,20,22	269:2 271:16
reviewed 12:4	89:1,3,9 94:21	221:1,2,3,5,7,8,1	272:19,20
72:3 96:13	96:15,19 99:16	1,12,15,16,17,19	273:4,8 275:16
285:4,6 312:6	100:12 101:7	,20,21	277:13,15,17
358:17	102:4 103:16	222:1,4,7,8,9,11,	280:22 281:17
reviewers 13:2	104:6,8,13,15,17	16,22 223:13	282:5,21 283:10
reviewing 328:2	,18 106:8	224:14,18,19,20,	285:10,19
re-worded 304:4	107:7,12	21	286:20 287:16
rhythms 93:13	108:7,14 110:8	225:1,4,5,6,9,18	288:7 289:9,13
Rich 365:10	117:21	226:10,13,15,19,	291:8 292:8,22
Richard 5:1 78:22	118:3,11,12	20	293:1 294:8
100:21	123:4,17	227:1,3,4,10,11,	295:17,21 296:2
right-hand 161:1	125:5,14,16,22	15,16,18,19,22	299:2,7,9,11
248:1	126:10,11,14	228:2,3,5,6,8,10,	300:2
rigorously 60:13	127:13,15	11,14,15,17,19,2	301:2,3,11,18
rimonabant 14:6	128:2,7,14,21	1,22	302:12,13,14,18
202:17 259:18	135:9 142:18	229:1,3,4,8,9,11,	303:7 304:1
270:16,19	143:2 145:4	12,13	305:3,19,21
271:6,19 272:4	147:22 150:14	230:18,21,22	306:7,14,15,17,1
274:7,17	151:17 152:7	231:6,8,10,14,17	9,22 307:5,8,21
275:1,22	160:4 164:11,20	,18	308:2,3,8,9,10,1
283:14,16	165:1 166:20	232:1,3,8,9,10,1	4,17,19
	167:15	1,16,17,18,20	309:10,11,17,21
	170:21,22 171:7	233:4,5,7,9,10,1	310:2,7,9,14,18
	177:22	1,14 234:7,8,21	311:15,22
	178:1,4,10	235:2	312:15,17
	187:15 188:8	238:17,18,19,21	313:1,3,5 314:22
		239:1,2,4,6,8,10,	315:2,11,13
		13,15,21,22	316:11,15,17,22

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 76

317:11 318:1,5 320:1,2 323:13 324:13 328:3,12 329:7,16 330:12,13 333:14 334:16 335:5 336:5,7 337:18 338:2 344:7 346:15 347:9,14,17 348:7 351:4 354:1,11,13,15 360:2,10,15 362:2 risk-based 334:17 risk-benefit 296:16 317:14 risks 13:16 14:13 17:3 21:2 52:16 123:7 187:18 188:1,4,6 205:15 209:16 210:4,19 216:8,9,10 219:15 271:20 284:9 341:6 roadmap 341:3 Robert 10:10 robust 276:6 296:5 301:2 315:12 357:19 Rochester 5:14 role 9:4,22 76:19 81:2,12 99:5 224:18 241:20 296:15 309:16 325:2 Romero-Corral 52:3 Ron 87:2 room 2:13 81:8	119:7 186:7 245:16 Rosebraugh 2:14,16,17 rosiglitazone 311:9 320:18 321:11 roughly 119:1 273:18 317:8 routine 314:9 row 50:5 225:18 royalties 9:3 RR 215:14 Rudy 364:9 rule 13:20 23:3 69:2 216:13 218:1,4 219:2 221:19 228:3,6,15 230:21 231:10 232:3 240:5,19 245:6 254:6 261:12 303:22 308:13 309:20 311:1,4 312:17 315:18 332:11 334:6 335:2 ruled 214:4 218:15 219:6 239:15 309:17 311:15 332:7 rule-out 38:2 rules 236:1,2 ruling 216:18 217:4,5,9,10,19, 21 218:2,18 219:8 227:2 run 12:19	run-in 175:11 203:15 259:8,14,17 260:1 265:11,13 269:8 366:6 running 72:4 RVH 89:14 <hr/> S <hr/> Sacramento 5:20 safe 199:3 safety 11:15 12:6,14 13:19 16:15,18 18:13,17,21 22:21 23:7 26:4,5,20 27:7 66:16 72:20 122:1 129:11 152:1,5 205:16 211:15,22 212:22 213:2 214:17 216:3 219:12,22 222:16,18,22 223:5,21 224:14,19 225:8,22 226:6,12 233:3 234:2 235:18 236:5,7,11 238:12,16 241:11,17 297:1 298:10,20 299:1,5,14 300:11 301:15 302:5,21 303:16 308:11 309:3,4,6 312:22 314:10 315:5,16 317:18 319:18 321:12,15 330:3	331:20 339:21 357:1 Sahlroot 58:9 339:5 Saints 93:17 sales 30:14 sample 21:15,19 23:6 28:1 30:10 34:3 223:3 224:22 225:11,13,20 245:13 251:17,22 284:12 363:11 Sanjay 3:3 103:19 satisfied 308:11 Satisfying 311:11 saturated 102:20 Savage 14:21 15:1 save 135:7 saved 54:9 saves 135:9 saving 134:16 135:18 saw 43:3 68:21 69:4 70:13 120:14 127:10 162:13 195:14 268:12 283:2 320:12 336:1 353:22 scale 133:16 134:19,22 scales 134:21 140:14 scatter 202:15 scenario 49:11
--	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 77

85:2 183:9 221:12 224:12 226:22 310:22 334:4 scenarios 221:22 230:11 236:22 237:10 244:17 schedule 53:13 117:1 scheduled 25:13 schematic 278:1 Schematically 306:11 scheme 22:14 310:3 School 4:10,17 5:11 schools 99:21 science 6:4 75:4 scientific 10:10 176:19 scientifically 350:9 scientists 75:3 90:2 score 171:7 scores 83:21 314:22 SCOUT 20:3 106:4,6 203:3 208:15 260:16 264:19 267:4 268:9 270:20 276:9 277:1 278:4 279:9,18 280:12 282:3,8 283:2 284:1,3,4,7,13,1	8 285:1 316:7 317:16 326:21 327:12 335:16 screened 8:18 screening 258:18 SDI's 33:12 se 80:13 85:20 87:8 91:4 93:4 second 16:17 18:16 26:11 41:18 47:10,15 69:14 76:18 151:17 176:10 189:11 193:15 195:4 198:6 222:19 233:14 244:4 246:3 265:6 270:19 273:8 294:15 302:2 307:7 319:13 secondary 25:18 147:11,12 177:2 181:18 Secondly 94:21 243:21 section 3:17 4:18 7:18 8:3,10,21 sectional 127:7 secular 151:16 164:2 secured 186:9 seeing 324:5 334:7 337:17 346:8 356:12,15 362:9 seek 12:12 63:15 264:13 seeking 296:21	Seely 4:9 55:4,5,19 56:7 109:3,4,13 326:2,3 seem 88:10,19 340:22 seemed 97:13 124:20 182:22 336:11 seems 53:3 57:11,16 73:13 75:3 82:9 88:3 102:13 105:21 110:19 166:11 208:19 269:2 324:2 seen 24:21 26:3 27:3 28:3,9 39:14 63:13 92:9 109:8 123:18 127:21 138:21 143:2,12 153:17 202:9 209:18 229:2 232:9 255:9,13 269:22 310:6,12 312:7,17 353:4 362:21 sees 197:11 select 123:16 176:7 207:7 289:22 346:10 366:11 selected 37:21 51:9 118:12 183:7 218:11 219:2 222:19 223:15 238:19 239:1 309:1,14 361:2 selecting 123:15 195:18 210:21	225:19 310:15 selection 123:15 313:4 366:4 self 51:9 self-fulfilling 267:7 send 267:8 sending 263:11 sensation 288:5 sense 13:6 53:13 59:22 83:21 132:1 162:13 182:16 198:14 252:15,19 269:5 273:20 329:1 364:2 sensitivity 25:7 41:15 44:7 45:16 59:20 79:13 80:8,12 81:2 103:10 112:8 145:20 246:16 sentinel 360:9 separate 108:7,13 133:21 176:22 217:16 256:11 separately 247:16 separation 274:22 275:21 September 368:7 sequence 112:13 sequentially 307:13 series 13:8 128:17 138:8 165:3 190:9 191:5 serious 92:18
---	--	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 78

201:13 274:8 serotonin 276:11 served 193:12 service 88:17 services 8:8 88:16 sessions 149:9 157:4,5,9 sets 251:5 307:2 setting 29:4 33:20 63:15 66:10 76:14 242:6 311:14 settings 9:6 32:1 38:5,7 65:8,10,12 several 12:4 15:5 47:5 91:13 135:22 137:13 147:11 154:9 167:22 176:20 185:18 187:17 188:17,20 190:7 198:9 202:4 208:13 210:18 223:4,11 235:8,21 243:2 259:21 310:16 312:18 319:21,22 366:7 367:22 severe 91:6,7 107:1 156:6 193:10 356:11 severely 61:12 155:22 156:1,10,14 342:15 347:13,15 366:18	severity 38:4 sex 23:8 141:21 sexes 124:5 share 79:21 84:10 182:11 183:22 184:21 185:3 239:16 322:7 she's 52:11 175:5 342:12 shift 138:15 318:11 shifted 41:18 45:18 shifting 78:15 shifts 318:12 short 48:8 60:6 69:21 70:8 145:17 226:9 265:5 shortcomings 294:1,10 shortening 94:5 shorter 45:10,12 48:9 335:14 shorter-term 335:12 shortly 203:5 short-term 40:9 48:12 142:6 145:16 206:13 showed 35:11,12 38:16,19 47:11 52:2 67:14 85:8 100:11 125:1,19 130:13 131:12 132:7 135:2 137:18 156:1 178:10 194:2,14	197:4 200:20 244:22 246:21,22 247:7 273:18 318:10 329:10 334:12 336:5 347:6 349:16 350:17,18 358:13 showing 69:20 91:3 94:8 121:5 124:5 136:9 138:20 145:15 153:10 154:14 165:3 166:10 179:21 188:13 189:21 190:16 200:22 205:20 221:15,16 224:21,22 229:15 233:9 242:1 247:6 274:20 296:5 297:3 333:6 346:7 366:12 shown 35:12 45:10 46:15 97:1 120:17 121:8,9,21 122:5,8 124:1 125:7 130:1 133:15 136:11 140:4 141:4 143:13,15 145:11 152:22 153:1 158:12 159:14,15 160:6 161:9 165:18 166:3 190:20 193:22 204:17 206:16 216:20 218:3 222:2,6 223:10 227:8	229:2 230:11,17 232:22 233:18 237:10 274:13 280:15 282:8 287:7 294:17 300:1,8 313:20,22 314:1,8,22 323:22 shows 30:19 31:20 32:11 35:3,8,14 36:17 37:4 41:2 44:17 46:3,19 63:13 117:12 120:7 130:9 136:2 148:15 161:13,22 162:3 198:10 229:3 231:20 232:10 362:15 sibutramine 14:6 17:19 20:4 31:12 32:8 34:11 35:4,18,20 36:3,10,19 37:6 38:18 40:4 60:22 110:7 200:21 201:3 202:17,20 203:5,16 204:1,2,5,12 205:1,7,20 208:15 245:1 268:17 269:10 270:20,22 276:9,10,22 278:5,10,17 280:19 283:4 284:2,17 317:16 324:15 348:16,18 354:14 Sibutramine-
---	--	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 79

<p>induced 276:14</p> <p>sibutramine's 98:5</p> <p>sibutramine-treated 204:20 205:8</p> <p>sick 363:10</p> <p>sided 279:11</p> <p>sides 259:19</p> <p>sign 72:1 98:4</p> <p>signal 109:6 185:15 271:16 285:11 302:6 303:16,20 325:12,16,17,18, 19,21 331:22 332:2,3,4 340:8,12,13 348:7</p> <p>signals 77:7 98:3 264:21 265:16</p> <p>significance 23:20 24:13 27:21 105:8</p> <p>significant 24:5 38:9 84:1 92:5,11 105:7 121:21 123:14 155:7,16 156:16 159:22 162:4,6,8,15,18 164:7,22 190:13 191:6 283:6 293:13 317:3,4 345:19</p> <p>significantly 17:13 159:18 161:17 190:18 281:20 309:18</p> <p>signing 172:9</p>	<p>signs 88:3 172:7 278:11 294:15</p> <p>silence 2:3</p> <p>Silver 1:17</p> <p>similar 12:3 43:3 48:13 125:18 126:12 130:13 137:13,14 161:22 162:12 205:21 220:6,16 221:16 222:11 230:11 247:6,9 282:2 287:5 288:22 294:3 298:6 322:6,7,15,22 335:19 337:10 358:14 361:4</p> <p>similarities 362:9</p> <p>Similarly 42:10</p> <p>Simons-Morton 104:11</p> <p>simple 60:4 292:1 326:17</p> <p>simpler 122:6</p> <p>simplest 72:12,15</p> <p>simplicity 219:16 292:10</p> <p>simply 84:10 91:5 98:10,20 100:1 112:17 137:22 171:10 274:20 278:1 325:20</p> <p>simulated 240:13</p> <p>simulation 240:9</p> <p>simultaneously 307:13</p> <p>Sinai 5:3</p>	<p>single 69:12 188:4 215:1 259:8,13,17,22 278:4 294:5 304:7 312:14 353:17 356:12</p> <p>sites 77:17</p> <p>sitting 349:9</p> <p>situation 107:9 251:19 285:5 318:4 359:18</p> <p>situations 49:8 57:12,15 329:21</p> <p>six 25:15 62:9 73:11 102:21 111:7,8 112:15,20 115:16,17 119:12 149:4,5 203:15,18 204:11 210:8 259:8 278:3,6 280:1,12 297:19 298:5 310:4</p> <p>six-month 298:21</p> <p>Sixteen 148:19 252:9,10</p> <p>six-week 265:4</p> <p>size 16:5,12 18:11,12 22:15 23:6 46:5,6 107:11,15 120:4 212:6 223:1,3,4 224:22 225:20 226:14 229:15,17 230:12 233:2,5,12,15,19 ,21 234:10 241:20 242:5</p>	<p>245:13 251:17,19 310:20 363:11</p> <p>sizes 224:1 251:22 284:12</p> <p>Sjostrom 194:18</p> <p>skeletal 80:7</p> <p>skewed 43:13 44:4 45:9 110:6</p> <p>sleep 21:12 60:10 84:13 86:5 189:13 193:17,20,21 194:5,9</p> <p>sleeve 199:19</p> <p>slide 12:17 28:1 45:11 46:19 49:5 50:16 55:6 64:5,21 65:5 79:1 82:6 83:10 85:7 89:4 91:3 92:1 93:4,14 95:22 117:10 118:5 128:16 148:15 160:12 161:13 163:5,8 177:4,9,19 178:10 179:13 188:9 189:5,20 195:4 197:4 201:18 202:4 203:21 205:6 206:15 217:13,14 221:6 227:13 236:20 237:11 246:22 247:13 248:21 252:8 253:20 267:3 287:10 289:14 292:17 293:9 310:16</p>
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 80

311:2 314:1,4 315:7 316:6 326:5,20 327:1 336:10 348:13 350:17 355:22 356:13 slides 60:9 88:10 158:5 160:14 165:3 166:9 190:20 193:17 218:3 219:11,14 229:14 235:8 236:19 250:19 268:14 296:19 301:7 307:17 311:17 sliding 238:18 slight 116:20 274:22 314:13 323:19 slightly 282:21 314:16 slope 126:13 slow 115:8 slowed 131:16 slower 215:20 small 46:7 60:7 70:11 81:20 107:22 108:5,8 133:16 157:17 159:6 226:2,8 276:1 287:16 329:6 345:17 363:22 365:5 smaller 22:20 43:13 48:17 126:13 219:2 235:19 256:13 287:12 335:12	smart 246:1 smooth 100:5 social 173:22 Society 53:7 sociodemographic 314:11 sodium 90:21 software 30:13 solely 237:12 286:2 solid 237:1 Solomon 144:10 solution 176:13,14 solutions 40:12 152:12 solve 139:1 solved 100:8 somebody 69:20 71:5 113:21 154:17 172:2 somebody's 208:20 somehow 171:13 247:14 364:19 someone 71:17 106:1 111:19 115:17 128:7 172:7,9 257:19 someone's 128:2 137:22 189:12 sometime 139:21 somewhat 44:9 48:17,18 87:19 95:3 102:1 125:18 208:3 338:15	somewhere 64:7 206:7 356:15 364:4 sophisticated 107:19 sorry 50:1 88:20 96:6 113:3 170:15 174:9 177:12 256:7 347:2 349:7 sort 54:13 58:2 59:21 60:5 62:21 108:21 133:1,16 162:7 258:13 262:22 269:14 316:14 324:12 329:7 332:18 334:1,3 349:12 351:9 353:7 357:20 358:19 359:22 368:7 sorts 172:11 189:8 SOS 93:16,19 97:1,5 102:6 104:21 146:5 367:4,7 Soukup 13:18 14:2 211:6,10,11 243:9 244:4,18 245:8,20 246:11 251:14 252:9 253:1,2,6,20 254:22 261:18 262:6 273:17 282:12 339:2 Soukup's 279:15 306:21 sound 178:15 sounds 64:7 72:22 244:3	source 30:3,9 34:13,18 40:12 sources 49:16 South 3:21 Southern 187:6 southwest 117:9 spare 185:8 speak 6:12,21 13:12 51:4,6 318:18 320:7 341:11 speaker 10:13 13:15 74:21 144:13 253:6 285:14 speakers 10:4,6,9 13:9 74:20 246:20 260:12 262:10 316:3 340:17 342:1,3,10 346:21 363:19 368:14 speaking 9:2 12:18 62:13 106:4,10 special 7:11 8:4,12 49:6 212:1 222:7,9 specialist 65:21 specialists 53:9,19 specialties 32:11 33:8 65:16 66:4 69:15 specialty 29:10 32:22 33:10 65:4,10,18 66:11 68:1 specific 11:7 51:6
---	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 81

116:18 134:1 169:11 186:21 202:13 227:21 228:13 231:4,21 286:8 288:14,17 289:1 299:7 301:16 302:10 305:6 320:8 325:14 326:11 340:19 specifically 120:10 127:2 170:8 188:21 189:15 281:6 287:1 292:16 299:2 307:1 309:14 326:17 328:8 330:10 speculate 70:13 spend 50:21 203:3 270:10 367:14 spirit 6:15 split 205:5 sponsor 267:17 297:5,18 299:9 305:1,7 306:2 312:1 317:21 328:3 329:10 330:11 sponsors 25:10,19 58:18,21 59:11 60:15 298:14 305:11 307:2 310:9,13,19 312:8,10,21 314:12 315:16 320:10,22 321:6 327:7 331:3 336:15 spouses 8:20	Spring 1:17 Spruill 3:19,20 64:18,19 65:13,16,19 squared 119:6 stability 102:15 112:3,7,16,18,19 113:15 115:10 stabilized 130:21 367:10 stabilizing 351:20 stable 120:18 130:14 131:3 165:10 191:12 stack 198:6 staff 79:5 174:2,5 186:10 stage 63:12 192:18,19 193:3 218:10 238:22 239:1,2,4,5,12 241:3 290:4 331:11,14,15 363:2 stages 192:18 193:10 staggered 121:3 stagings 192:17 stair 89:1 staircase 78:7,8 stair-step 121:12,19 stand 2:7 116:11 standard 58:12 119:16 120:9 123:12 168:1 222:17 265:21 271:4 284:5	285:9 300:9 301:21 303:9 315:9 321:20 322:4,6,21 323:14 standardize 299:3 standardized 313:9 standardizing 305:16 standing 9:15 256:14 standpoint 52:14 53:2 281:19 stands 202:19,21 300:4 337:1 star 220:22 221:18 238:21,22 start 2:13 15:15,17 46:14 68:18 72:21 115:10 137:4 139:5 143:10 160:19 161:8 183:13 246:20 265:15 270:8 286:1,4,13 293:8 304:12 341:4 342:1 344:1,13 349:12 366:17 368:5,8 started 42:10 127:2 129:14 141:7 142:20 150:21 160:21,22 163:12,15,18 250:4 271:22 321:4 347:15 starting 28:8 139:3 141:12	152:2 161:10 186:17 272:17 356:4 368:3 starts 41:19 75:18 160:16 starvation 77:9 state 18:3,7 80:18 194:10 330:10 stated 15:22 290:20 292:1 297:2 statement 62:13 72:13 143:21 252:4 304:8 statements 9:16 351:17 352:12 states 20:20 21:14 23:22 25:2 39:17 70:7 99:22 118:9 123:3 289:16 290:17 291:4 346:11 statin 104:8,13,18 166:18 342:13,22 343:4,7 344:1,13 362:19 stating 264:17 statins 104:6 163:13 164:17 166:12 344:21 345:2 346:2 351:22 statistical 13:18 23:20 24:13 27:20 38:8 58:3,8 105:8 136:21 211:14,20 212:4,7 213:19
--	--	--	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 82

215:4 216:4 234:10 236:18 241:16 242:17 243:3 263:1 281:19 306:3 311:21 330:19 statistically 20:13 24:5 25:1 38:9 162:15 164:7 214:15 220:4,14 244:5 245:20 261:20 283:5 317:4 345:19 statistician 4:2 5:8 statisticians 301:14 statistics 53:5 54:1 58:9 225:10 306:16 status 7:15 31:11 72:9 280:8 stay 63:20 67:8 76:9 158:19 161:3 179:17 332:19 346:22 stayed 42:1 45:4 50:9,14 140:17 171:2 278:22 stead 56:3 steeper 78:9 steering 171:16 step 332:11 steps 149:22 315:15 stick 54:6 sticking 276:7 stigma 189:12 stigmatized	209:20 stockpiling 41:17 44:8 stop 71:6 95:14 263:4 264:14 267:19 351:2 365:12 stopped 20:11 176:20 272:12 274:7 280:12 281:6 295:17 349:14 stopping 161:12 210:21 stops 164:1 story 103:22 straight 204:14 strategies 25:8 149:12 198:11 210:19 336:11 338:12 strategy 77:18 265:8 270:1 318:15 337:12 strengths 149:10 stress 155:8 strict 272:9 277:6 282:22 stricter 155:4 strictly 14:18 striking 328:17 string 40:22 stroke 36:13 37:11 39:9 85:10 93:6 147:9,14,15 190:20 204:17 213:9 253:17 272:8 274:2	277:4 281:1 291:8 300:7 336:6 strokes 75:6,21 94:18 138:5 strong 127:6 142:1 165:17,21 257:10 352:21 stronger 318:22 strongest 159:10 167:8 strongly 6:7 141:22 143:1 178:11 struck 64:21 257:14 structure 325:10 structured 149:18 struggled 253:7 struggling 359:9 stuck 316:12 students 79:6 studied 16:14 23:10 27:4,17 106:18 236:14 364:3 studies 15:3 16:13 19:19 21:15 22:16 24:22 26:18 27:15 89:6 107:14 109:15 127:7,21 131:6 135:22 136:7,20 137:2,8 138:11,20,22 143:12 145:15 146:3,5,8 150:16 151:19 152:16 163:19 169:3	174:2 177:3 185:18 188:10,12 196:12 197:10,21 198:6 249:21 264:12 292:6 297:6,8,10,19,20 ,22 298:7,8,16,21 299:1,8,10 301:1 304:10 306:22 308:22 311:21 312:4,12,20 314:10 321:3 334:14 335:12 336:19 343:14 346:5 358:2,5 362:15 365:11 studying 56:22 318:16,20 362:1 subcutaneous 77:12,15,17 subfractionation 107:18 subgroup 193:19 273:8 316:6 subgroups 23:8 258:15 273:4,9 275:13,15 277:16,22 281:10 306:1 316:16 317:12 subject 7:13 212:16 236:14 237:2,3,15,21 subjective 181:20,22 183:16,19 subjects 23:22 25:3,11,14 64:8
---	--	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 83

71:12 129:22 190:9 191:11 195:6 212:5,12,15 214:15 215:3,19 217:7,12 235:13,16,20 236:9,11 277:2 278:4 279:20 280:5 283:13,15 284:14,20 287:13 289:9 291:10,13 295:15,21 296:3 297:11 298:15,17,18 299:18 300:2 301:1 314:5,17 357:5,12 submit 52:12 183:8 196:14 submitted 312:6 335:18 subsequent 112:20 122:13 141:22 201:2 219:14 233:20 263:21 subsequently 17:17 257:22 subset 26:8 37:22 subsets 159:22 substantial 76:12 89:9 193:7,9 269:1 substantially 132:5 200:6,9 231:19 248:1 310:20 substrate 100:2 subtracted 24:10	196:15 250:22 251:3 271:10 276:17 subtracting 250:13 succeed 264:15 success 124:21 144:18 154:5,19 209:1 210:8 258:19 357:5 successful 94:6 154:17,21 155:2 159:12 173:18 209:10 sudden 49:13 86:18 106:14,19,22 321:17 suddenly 68:5 sufficient 20:22 22:11 56:18 305:20 326:18 331:4 340:2,9,10,11 sugar 103:16 138:1 346:2 suggest 19:19 146:3 181:2 188:6 317:22 suggested 118:5 146:6 296:11 299:9 304:8 311:13 320:14 328:5 suggesting 159:1 261:6 suggestion 109:17 suggestions 209:15 210:14	264:4 suggests 143:5 215:20 291:10,15 295:1,8 suicidal 202:1 suicidality 26:14 271:16 suicide 336:7 suicides 274:9 sulfonylurea 289:20 294:17 296:12 summarial 111:17 summarize 48:7 201:18 232:22 241:15 271:5 284:6 summarized 128:16 summarizes 307:16 summary 15:12 27:10 30:1 38:10 39:19 sun 258:8 Sunshine 6:16 superior 297:14 331:12 superiority 220:7 273:14 279:12 284:10 298:3 302:12 supply 29:18 36:4 40:20 41:1,13,19 43:16 47:17,21 48:1 55:17 support	18:14,16,18,22 147:4 150:1 163:4 193:1 308:6 suppose 60:10 216:18 218:13 219:4 320:5 supposed 52:19 suppressants 114:12 sure 13:22 41:5 42:19 50:17 67:20 70:22 87:17 90:14 97:15 100:7 109:12 113:22 115:2 144:2 179:18 250:3 258:8 269:20 326:4,15 331:19 334:19 338:16 340:5 343:5 355:7 surgeons 206:10 surgery 93:15,21 96:21 97:6 101:16 112:17 199:12 255:11 367:5 surgical 146:2 190:8 191:5 199:13,18 200:7,13,14 surgically-treated 190:19 surprise 155:20 surprised 64:22 122:21 346:6 350:5 363:22 surprising 11:21
---	---	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 84

65:2 314:17 surprisingly 134:3 surrogate 54:15,17 68:13 96:13 111:4 266:13,15,16 surrogates 54:21 surrounded 42:14 surrounding 301:10 surveillance 13:2 28:15 144:12 348:1,8 survey 33:15 53:7 survival 215:22 susceptibility 140:2 susceptible 291:11,18,19 suspect 73:17 90:13 367:18 sustain 349:14,18 sustained 166:14 167:4,10 170:11 236:4 349:19 Swedish 190:9 191:11 switch 135:21 195:5 234:9 switched 195:6,9,10 switches 30:12 31:12 sympathomimetic 279:2 318:22 symptoms 121:16 287:22 292:17	294:14 syndrome 76:3,8,11,12,20 77:21 80:1,6,19 84:3,6,9 86:7 107:6 272:21 336:17 system 91:2 94:14 135:10 190:22 systemic 80:6 81:4 systemically 81:3 systems 30:13 287:20 systolic 91:6 93:10 161:22 165:20,21 166:15 167:11 179:21 184:11,17 191:19 <hr/> <div style="text-align: center;">T</div> <hr/> table 2:15 121:8 131:12 136:11 201:13 216:20 227:21 228:13 229:6 231:4,20 232:13 307:16 313:15 315:15 362:12 tachycardia 97:20 98:1 Takeda 187:12 take-home 166:22 taking 39:5,10,14 64:12 68:3,11 75:6 268:13 352:8 talk 13:21 15:15	73:17 85:15 95:18 97:18 102:18 117:4 138:16 139:4 145:1 175:5 177:2 187:15 189:14 269:12 279:8 285:18 306:21 309:13 315:19 333:21 337:19 343:12 354:7 359:14 talked 49:6 54:19 64:21 65:6 103:9 171:21 179:12,13 189:9 192:9 327:1 328:18 talking 50:7 88:20 124:7 126:19 136:3 138:21 171:22 255:7 264:18 265:19 275:6 286:2 293:8 363:7 366:8 talks 347:1 tap 12:20 target 230:12 274:15 279:12 288:14,18 359:16 360:2 targeted 230:4,8 242:11,14 273:14 280:14 targeting 17:2 242:12 targets 216:11 TCF7L2 127:4 teaching 9:2	team 58:9 211:11 285:16 tease 126:3 178:12 techniques 120:9 173:13 199:13 215:22 technology 107:20 Temple 6:1,3 73:19,20 74:10,13,17 258:12,13 269:7,11,18 322:12,13 323:3,20 331:9,10,17 332:5 360:20,21 363:4 temporal 112:13 temporary 7:10 8:1,17 9:11,15 10:15 tend 202:13,22 235:11 250:8 268:5 319:8 348:3 tended 131:14 tendency 132:19 tends 83:4 107:1 term 16:2 49:22 51:18 53:21 54:2 113:10 130:5 145:17 159:12,13 199:6 205:20 303:21 317:2,4 338:15 terminated 274:10 336:3 termination 122:2 129:9
---	---	---	--

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 85

terminology 76:4	243:17 307:12	165:10	20:20 200:1
terms 17:5 18:22	tests 38:8 121:18	168:17,20	293:20 305:2
20:6 34:2 57:20	155:9	169:15 172:7,8	309:7 321:13
60:16	thank 7:4 11:2,10	173:1 177:8	324:8 326:11
72:12,13,16,19	14:20 15:7 28:13	179:5,9 183:15	therapy 16:22
77:11,12 79:1,11	48:21 54:5,9	193:12,17	23:15 74:14
89:2 92:1 95:9	63:9 69:17 72:11	196:14 198:4	104:18 198:14
98:10,16 100:19	95:14,17 96:9	205:17 206:13	199:13,15,21
105:12 106:8,10	103:9 105:15	244:14,20	200:4 210:6,20
108:14,19 110:9	109:2 116:2	247:16 249:6	222:17
114:1 126:3	144:6 168:8,9	251:6,12 254:10	290:10,11
129:2 134:14	186:14 187:1	255:14 257:5,9	297:13 298:2
145:1,3 154:15	211:3,5,10	259:12 260:11	303:15 321:5
156:9 159:17	243:4,7,11	261:3,18 263:15	322:9 351:21
168:2 180:11	245:10 258:12	264:10,15 267:7	353:1,6,11
190:3 193:4	285:13	268:20 269:18	362:19
229:15,17	315:20,21 336:9	279:7 318:14	thereabouts 259:6
230:12 241:1	349:10 351:13	322:3 328:9	thereafter 208:7
242:8 243:15	352:16	330:16 331:4	370:5
244:12 245:12	368:13,17 369:5	332:18 338:7,10	therefore 20:11
252:3 277:13,16	thanks 99:3	340:10 341:2,18	25:21 41:7 83:10
287:6 290:15,22	101:11 255:1	344:4 347:3	146:9 210:11,14
291:12 298:13	326:14	350:11 351:9,12	212:9 214:2
300:13 306:6	that'd 332:3	353:16,20	226:11 236:13
311:12 313:16	that's 28:6 50:1,16	354:14 358:22	238:9 300:12
319:3 322:9	52:10 55:18,19	360:18	308:5 317:1
328:11 330:9	56:9 57:14,17	361:12,20	340:4
343:12 356:14	61:1 63:7 65:11	363:4,13,14	there's 49:8,21
359:10	70:12,16 72:21	365:1,13,19	54:7 57:12,13
terrible 176:1	73:4,5 74:6 84:4	366:21	72:22 73:1
tertiles 78:6	87:16 93:19 94:2	themselves 10:20	83:3,10 85:5,15
141:20	96:5,11 99:15	54:8	86:17 87:21
test 119:13 121:14	100:18 101:2	theoretical 353:7	103:2 114:15
152:2,4,6	102:1,16,19	theoretically 257:9	123:14 124:15
244:13,14	104:19 112:8	334:8	132:19 154:10
267:22 307:2,11	114:16 118:16	therapeutic 17:2	157:17,21
309:15	121:8 129:2	289:15,22	158:1,3 160:18
tested 244:14	132:8 136:11	293:16	164:16 176:2
testimony 9:1	138:9 144:17	therapeutics 293:9	187:20 188:14
370:10	145:15 152:8	296:14	189:11 193:9
testing 118:9	153:9 157:10	therapies 11:18	196:22 207:3
	159:14 164:17		211:1 233:6

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 86

240:14 241:21 244:7 248:10,16 254:1 268:18 278:16 281:16 321:17,19 322:9 325:3 327:8 331:18 332:17,21 333:2 340:3 343:5 346:2,3,12 348:1 349:11 351:1,3,19 353:2,3 355:19 359:19 362:16 363:17 364:6 366:22 theta 230:5,9 they'd 278:19 they'll 145:19 361:14 they're 12:17 65:10 94:16 99:4 108:17,18 110:20 114:1,7 116:9 119:2 123:12 161:20 164:8 167:3 172:7,10 173:20 189:13 198:8 202:1 205:11 207:3 250:10 257:7,16 264:2 265:9 266:9 278:16 279:4 282:11 316:12,20 322:10 325:21 331:13 333:22 343:18,21 344:1 352:7 364:7,13,22 365:15 366:13	368:3 they've 14:19 73:3 149:5 154:18 187:20 251:4 362:22 thin 117:19 third 26:13 45:20 48:14 64:7 119:21 147:16 302:3 Thirdly 95:1 third-party 32:15 67:17 thirds 30:16 69:12 Thirty-six 274:1 Thomas 2:2,9 4:4 6:1,5 11:3 14:20 15:7 28:17,20 48:22 50:3 51:15 54:5 55:4 56:14 57:8 59:7 61:9 63:10 64:2,18 66:12 67:22 68:13 69:17 71:7 73:18 74:18 95:17 96:10 97:17 99:2 101:10 103:8 105:16 106:13 107:4 109:3 110:14 111:18 113:1 116:2,14 144:6,13 168:9 170:2 171:18 174:8,11 176:17 181:12 184:22 185:5 186:1,16 211:5 243:7 245:9 246:18 251:13 252:22 253:4 258:12	260:6,10 262:8 264:8 266:2 267:1 270:2,8 285:13 315:21 321:9 322:12 324:10 326:2,13 329:18 331:9 332:19 334:10 336:8 340:14 341:21 346:20 347:3,19 349:6 351:14 352:14,17 354:21 357:3 358:8 359:8 360:20 363:16 367:12 368:12 thoughts 243:14 258:18 thousands 31:21 three-month 111:11 112:14 three-year 130:13 threshold 117:21 214:11 220:21 245:2 250:5 306:18 341:7 thresholds 292:6 thromboembolic 86:12 thrombotic 80:18 throughout 31:17 32:19 33:18 140:5,18 149:2 280:4 thus 6:11 142:12 152:5 312:5 tight 295:8 296:2 tighter 243:19	time-to-event 234:16 tissue 76:15,19,22 77:11,15,19 78:12,15,21 80:2,13,16 91:4 tissues 77:11 today 11:12 12:20 15:12 54:6 74:19 75:4 78:3 84:12 89:16 102:18 110:18 116:9 129:3 133:7 143:14 153:10 186:4 192:15 211:13 233:20 239:11 253:10 268:4 289:20 301:13 316:3 320:6 325:3 351:16 363:19 368:13 today's 6:6,8 7:6,20 116:20 369:5 Todd 58:9 339:5 tolbutamide 296:11 tolerability 290:5 tolerance 79:15 104:16 119:2,12 121:14 139:21 249:2 tolerate 261:9 tolerated 309:9 tomorrow 54:7,9 73:17,21 74:19 110:16 243:13 258:8,9 260:7,12,13
--	--	--	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 87

269:12,21 279:8 283:11 285:8 324:21 325:9 332:19 334:22 338:13 340:16,18 342:4 360:19 362:12 365:4 368:16 369:1,4 tomorrow's 14:8 259:4 362:5 tone 15:21 top 79:19 165:19 166:3 171:11 202:10 352:2 topic 6:18 7:3 9:17 73:16 75:7 87:16 116:5 117:11 133:6 238:14 270:4 368:22 topics 6:5 16:4 136:3 301:6 topiramate 202:6 total 31:3,20 32:17 33:11 97:16 105:6 120:4 124:13 181:3 190:18 236:21 237:6,14 239:5 241:7 242:19 261:2 282:13 286:19 314:4,7 348:17,22 349:3 totality 294:4 totally 151:5 173:22 247:12 touch 286:8 touched 278:2,21 342:12	tough 58:6 106:19 108:21 towards 45:19 141:3 180:2 182:1 toxicity 208:18 tracking 355:15 tradeoff 261:10 traditional 213:6,11,22 214:2 289:8 292:21,22 303:7 trail 114:16 trajectories 157:13 trajectory 20:15 Tran 4:7 7:5 12:16 transfer 83:4 transferring 83:5 transition 129:12 229:16 translate 230:3 transparency 9:14 travel 169:14 treat 11:15 12:14 13:16 16:7 27:4 28:16 49:22 52:19 53:1 55:13,18 56:5,8 59:2 143:20 194:13 205:2 208:14 282:10 285:20 288:18 290:3 293:10,11 296:17 326:11 treated 17:12 18:8 127:14 145:18 204:11 215:3	217:7,11 242:22 268:8 288:11 321:18 324:1 346:2 treating 53:22 55:11 118:10 126:21 129:19 207:8 209:12 289:21 treatment 9:7 17:4 18:1 21:2,3 23:14 25:6,15 28:5 33:17 53:8,18 56:3,16 57:15 63:15,21 68:7 71:12 91:14 119:15 122:8,16 126:15 127:16 128:10,11 129:5 131:22 132:15 133:14 134:3 135:5 143:19 159:3,7 174:1 182:6 187:10 198:12 200:15 203:19,20 204:10 210:17,20,21 211:16 215:18 225:8 234:18,19 235:20 236:3,10,12 237:2,3,8,16,18, 21,22 238:13 239:20 242:19 248:15 249:12,13 251:21 253:14 254:2,13 259:10 271:8 275:3,10 276:6,12,20 280:5 281:19 282:1,4,13,14,16	286:3 289:16 297:12 323:12 343:19 353:15 361:6 364:17 365:16 368:4,5 treatments 124:2 211:21 215:9,13,19 216:4 tremendously 357:17 367:6 trend 164:2 343:2 trends 13:4 29:3,7 151:16 trial 13:14 14:9 15:6 18:15 20:3,22 23:12 24:18 25:13 51:13 71:11,17 72:10 104:2,5 106:4,10 108:18 118:8 132:3 144:16,17,20,22 145:6 146:15,17 148:4,16 149:2,7 151:18 152:5,16 156:2,18 162:18 163:1,14 171:5 176:13 188:4 192:8 193:13 194:17,19 196:9 199:12 203:4,6,10,14 206:17 208:15,16 212:2,3,6,7,9,12, 21 213:20 214:9,12,13,16 216:11,13 218:4,10,13 219:4,13,22 220:7,13
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 88

221:7,13,14,20	352:3 353:20	264:1,21 265:3	43:5 54:15
222:7,8	357:6 358:15	270:13,14	165:18 172:18
223:4,6,12,17,22	trialists 184:3	271:3,4 274:7	176:9 223:13
224:11,12,13	trials 12:8 13:20	275:7	224:5 225:15,17
225:11,14,21	14:5 15:6 16:5	283:14,16,22	226:13,15,20
226:2,12,14	18:11,12	284:2,5,8,10,17	227:3,10,15,18,1
228:21	22:1,6,10,17	294:19	9,22
229:15,17	24:12,14 25:12	295:8,19,20	228:10,16,19
230:4,12	26:3 27:1 50:20	297:22 303:3,4,8	229:1,4,7
233:2,3,5,12,15,	58:16 60:16	305:10,12	230:18,22
17,20,21	61:14 71:2 72:4	306:4,5 312:3,9	231:6,8,16,22
234:10,12	99:6 137:13	315:9 319:8,21	232:9,11,18
235:12,15,19,20	142:20	320:10,11	233:7,14 239:21
236:4,11,13	146:1,11,12	322:5,15 336:18	240:6,10,14,19
239:3,10	152:14 159:14	337:20 342:18	241:22 245:11
240:5,18	164:12 167:19	344:7	310:1 345:17
241:2,8,18,20	168:2 169:1	346:7,11,19	349:15 351:9
242:5 256:2	170:1 171:21	353:19 355:5	363:9,14 365:2
258:15,21 259:6	173:10,11,14	356:2,17	370:7
263:9,17,21	175:11	357:5,10,16,21	truly 240:9 317:7
264:12,19	176:6,7,8,9	358:4,13 359:2	Truman 3:15
265:18,22	180:16,17 181:1	366:6	trumped 107:16
266:13	182:10 183:2	tricky 351:17	truncate 134:21
267:4,18,21	184:7 194:14	tried 123:2 125:22	truncated 41:6
268:9,12 269:5	196:20 198:1	133:21 167:12	274:14,18
270:19	200:22	201:18 251:5	try 14:18 54:6
272:11,17	206:18,22	256:22	71:18 113:12
273:5,14,21	210:11	triglyceride 82:17	135:16 139:4
274:14 275:16	211:15,20,22	83:2,13 103:12	144:21 146:11
276:10 277:1,7	212:1 213:1	191:18 271:12	149:15 173:21
279:12 280:4,10	214:17	triglyceride-	178:12 260:13
281:7 283:18,21	222:12,14,16,20,	lowering 104:2	276:5 285:10
284:1,4 285:6	22 223:21	triglyceridemia	340:19 341:22
294:21,22	224:5,9,14,16,20	82:19	343:12 365:8
302:1,11,13	226:1,2,5,8	triglyceride-rich	367:20
303:6,18,21	233:3,8,10	80:3 82:4	trying 61:17 65:14
304:8 312:3,13	234:2,5,7 235:11	triglycerides 108:4	72:16 128:9
313:1 315:18	236:1 238:12	148:11 276:15	173:5 174:15
317:16 319:10	241:12,13,17	troublesome 324:3	176:7 199:9
321:7 323:11,21	242:1,2	true 38:2 39:16	230:21
324:15	243:15,22		248:11,12
325:13,14,21	250:4,6 258:3		
326:1 336:2,4	261:21 263:7		
344:16 346:18			

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 89

254:7,16 320:1 362:5 Tufts 3:9 187:5 tuned 332:19 turn 19:3 58:7 81:16 91:22 114:22 153:5 160:3 233:21 243:5 275:5 288:2 292:3 turned 178:22 turns 218:8,17,22 Twenty-two 50:18 twice 172:3 311:3 337:11,12 twisting 263:11 two-and-a-half- fold 90:11 two-day 11:13 12:12 two-sided 224:6 227:6 230:15 273:13 two-stage 238:15,16 239:7,17 two-thirds 44:2 45:2 70:16 291:16 two-tiered 309:1 two-year 263:15 type 11:20 13:13 15:3 66:9 67:22 68:19,22 69:8 79:15,18,20 85:2 104:8,15,18 117:4,12 118:4,9,13 123:7	127:12 128:4 137:16 141:8,10 142:10,15 143:2 145:10,14 146:22 148:5 172:6 180:1 195:16 223:12 224:3,5,8 227:6,14 228:9 230:15 239:13 246:1 272:20 277:14 284:19 285:20 286:3 287:3,8 289:21 290:8,17 294:16,17,22 295:21 296:22 297:11 301:18,19 302:9,17 305:2,6 311:20 326:12 333:11 types 40:14 102:8 153:16 164:12 169:16 173:3,6 182:15 285:22 286:1 312:4 335:6 typewritten 370:6 typical 28:6 56:1 183:9 225:22 283:19,22 284:16 285:6 296:20 typically 24:21 52:6 132:17 146:3 151:18 163:12 175:10,18 222:22 224:15 236:6 264:16 297:7,20 298:8	<hr/> U <hr/> U.S 17:18 30:8,15,17,22 31:1 33:18 47:14 U.S.C 7:18 8:3,21 UCLA 187:6 UKPDS 294:22 295:8 ultimate 54:21 342:15 ultimately 15:20 16:7 22:13 75:15,16 76:1,13,16 77:5,6,7,8,18 79:3,15,22 80:13 81:1,13 82:13 85:3 88:1 89:8 90:5 91:1,16,20 93:18 94:4,5,10 97:7 98:11,19 100:1,2 102:13 103:21 104:2 111:20 114:12 140:3 142:17 143:10 215:18 240:11 241:13 261:18 umbrella 85:11 unable 307:19 317:21 unacceptable 261:6,13 262:4 303:22 305:4 306:19 308:2 341:5 unapproved 296:14 unblind 171:13	unblinding 171:3 uncertainty 306:15 308:3 309:8 317:17 329:4,7 uncharacterized 302:20 unclear 97:7 uncommon 46:8 uncontrolled 97:9 298:12,22 underappreciated 100:18 underestimated 48:6 undergo 302:4 underlie 243:13 underlying 205:13 290:8 318:13 361:21 underneath 84:1 underrepresented 306:1 understand 59:14 87:13 102:11 111:14 135:15 192:12 207:2 216:7 225:7 235:9 246:4 247:12,16 249:4 255:18 324:18,21 355:8 understanding 20:1 49:18 58:20 64:4 207:4 243:16 248:14 262:3 356:1 understood
--	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 90

256:15 334:19 364:2 unequal 251:22 unfortunately 12:16 51:13 63:22 133:8 137:20 138:6 153:15 unhappy 354:19 uniform 124:3 uniformly 123:13 uninformative 104:5 Union 272:1 unique 40:15 241:10 United 70:7 118:8 123:3 289:16 290:16 291:4 346:11 units 188:17,20 199:20 unity 222:10 227:4 Universite 86:21 University 3:7,12,14,21 4:21 5:6,11,18 28:21 187:6 296:12 unknown 34:5 40:18 225:10 233:15 240:9 320:16 unless 73:6 115:20 233:6 241:20 248:8,10 254:20 unlikely 268:20 366:9	unmasked 122:1 129:20 unnecessary 111:22 unpublished 94:8 unrelated 88:11 174:1 unresponsive 210:22 unstable 213:13 313:10 unsure 354:5 untreated 287:22 unusual 115:17 updated 103:15 upon 212:19 214:1,2,18 215:4 222:21 224:15 237:13,14 239:8,10,16 260:15 282:5 339:18 350:2 upper 44:5,13 84:19 101:6 132:8 221:8,9,19 222:3 234:22 240:15 241:5 245:2,7 307:21 308:17 316:19 326:16 327:13,20 328:20 329:12 330:16,18,20 335:2 338:22 339:9 340:2,9 341:13 upper-body 76:14 upstream 288:10,13	uric 191:18 usage 53:4 useful 60:6 96:9 292:9 293:20 user 44:3 users 43:2,5,6,7,8,11,1 4 44:2,5,21 45:3,4,12 46:3,16,22 47:1 148:19 155:19 163:15 207:22 usual 331:22 332:3 usually 297:5,12,19 298:6 299:1 321:3,6 322:8 328:10 338:7 361:9 366:7 368:2 Utah 93:17 utero 141:2 utilization 13:4 29:3,7,13 30:19 31:13 35:6 38:16 64:15 utilize 84:7 96:22 utilized 213:10 238:22 239:7 <hr/> V <hr/> VADT 295:19 vague 338:17 valid 246:10 292:15,20 301:21 311:14 validations 39:16 validity 303:6	323:21 360:1 value 87:21 105:6 212:18 218:6 220:21 225:15,17,19 226:13 232:9 233:17,18 281:21 285:9 339:10 values 109:14 140:10 227:22 228:14 231:5,21 233:21 valve 325:3 valvulopathy 17:19 Vanderbilt 5:6 VAP 107:19 variability 93:11 109:8,9,18 110:1,10 181:21 variable 163:2 250:18,20 298:6 351:1 variables 105:7 108:20 159:4 190:12 191:15 351:18 variance 159:7,8 variation 125:3 126:7 varied 357:17 variety 6:6 66:14 196:3 201:16 364:9 various 19:17 21:16 24:12 30:13 31:8 40:13 60:6 101:13
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 91

156:17 178:13 191:14 192:20 208:22 215:5 217:17 227:17 229:1,7 231:22 292:7 vary 22:5 101:14,15 210:10 227:16 235:12 282:5,6 358:1 varying 232:8 vascular 81:12 100:6 133:5 147:19 189:1 190:22 vasodilatation 87:22 88:3 vast 32:4 43:15 64:6 354:2 Vector 30:4,5 venostasis 86:11 ventricle 85:22 89:14 ventricular 85:17 86:1,17 88:4 91:7 93:9,10 94:4 versa 27:9 versus 17:11,13 56:22 65:21 67:8 77:12 78:6 90:10,16 100:11,12,20 105:12 197:1 243:22 247:1 266:5 274:17 284:2,5 316:15 323:7	vessels 288:6 vetted 184:20 via 113:6 vice 27:9 vicious 142:4 Vicky 29:2 55:5 Vietnam 89:5 view 54:14 58:17 62:12 137:9 198:13 views 6:10 virtually 352:22 visceral 76:15 77:12,17 78:21 101:6 vision 288:4 visit 34:1 169:12 visits 34:6,7 131:9 134:10 153:8 169:11,19 172:19 349:21 vital 72:9 278:11 280:8 vitals 236:4 VLDL 81:20,22 volume 30:17 31:18 88:2 90:21 93:6 volumes 94:5 voluntary 298:12,22 vote 10:14 voted 303:13 304:1,2,9,11 voting 7:10 8:1,17	9:11,15,21 10:16 vulnerable 296:4 <hr/> W <hr/> waist 78:6 272:15,22 277:12 wait 329:15 344:2 345:4 waivers 8:4,12 9:12 walk 160:12 257:1 walking 87:11 124:20 149:20 wall 81:6 92:8 100:4,7 108:11 352:4 Walter 189:20 ward 79:6 ware 38:6 washout 297:13 wasn't 60:20 178:5 179:7 190:9 265:22 268:1 Waters 4:20 171:18,19 172:22 wavelength 326:15 ways 25:1 75:1,3 99:17 143:14,20 144:4 149:13 172:15 344:15 350:4 364:9 weaker 98:21 weakness 99:9 wears 321:5	we'd 112:19 154:5 205:17 267:19 269:4 363:18 wedge 93:8 week 23:13 102:22 124:20 133:13 149:21 199:9 weekly 149:3 weeks 53:14 102:21 112:15 150:8 175:18,19 203:15 206:21 259:2,8,14 278:4 297:15 367:17 Weide 3:13 weigh 301:9 weighed 137:5 250:6 weighing 261:3 328:12 weight 11:22 15:13 16:9 17:4,7,10 18:4,6 19:7,8,12,16,20 20:8,11,12,15,21 21:1 22:5,8,12,20 23:11,12 24:2,8,10,11,22 25:5,10,16,20 26:9 27:3,4,7,8,9 49:7,9 50:8,11,15 51:1,12 52:11,13 54:14,17,22 55:7,12,20,22 56:7 57:18 59:13,15 60:14,17,21 61:4 65:15 66:8,10
--	--	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 92

69:22 71:1 74:3,14 75:12 77:8 90:17 93:5 94:2,6,13 96:14,18 97:5 101:13,16,19 102:2,10,11,12,1 5,19 103:6 109:6 110:22 111:1,6,8,16,20, 21 112:2,3,6,7,9,10, 16,18,19,21 113:6,7,15,20 114:2,4,19 115:5,9,14,15,18 ,21 118:3 119:7 120:7,9,13,14,15 ,18 121:1,7 124:9,11,16,22 125:1,4,6,7,11,1 2,14,15,20 126:1,4,7,8,9,11, 15,20 130:5,10,15,18,2 0,22 131:2,4,6,7 132:7,16,18,20,2 2 133:2 136:6,8,9 137:2,3,4 140:8 141:20,21 143:4,14,17 145:2,13,16,18 146:2,4,6,10,19 148:14,19 149:15 150:11 153:21,22 154:3,5,7,8,12,1 8 155:1,16 156:7,9,10,17,20 157:2,10,15,21 158:3,7,16,22 159:5,9,10,11,17 ,19,22 160:2	164:21 165:8,13,22 166:5,8,12,20 167:4,6,7,9,19 168:2 169:6,18 170:4,10,14,16 174:15,17 177:1,17,22 178:2,3,11,13,16 ,17,20 179:2,7,8,15 180:3,8,15,18,21 181:6,10,11 185:11,21 187:16,18 189:17 190:6 191:9,10,12,20 192:1,3,7 193:11,22 194:1,11,15,16,2 2 195:1,9,10,16 196:4,8,9 197:3,5,10,13,16 ,18,22 198:18,22 199:18,21 200:7,19,20,22 201:2,4,6,7 203:22 204:1,2,6,8,12 205:6,8,9,12,21 206:6,9,14,17,20 ,22 207:5,7,10,11 208:10,11 209:2,5,8,15,16, 21 210:2,11,12,18 211:17 247:1 248:1,3,10,11,13 ,17 249:2,7,8,10,16 250:5,7,10,22 251:6,9 253:10 255:7,12,16	256:3,10,16,19,2 0 257:5,6,9,11,12, 15,21 259:11,15 260:4 261:12,14 263:5,6,9,22 264:20 266:20 267:5,6,20 268:4,6,16,18 269:1 270:21 271:10,11 276:13,14 278:7,11 279:1,4,5,6 284:9 335:21,22 343:18,22 344:2,3 347:8,14 349:13,14,18,19 350:5,6,8,10,16, 19 351:6 352:2,21 353:5,10,19 354:3,10,11,19 357:19,22 364:1,4,9,12 365:2,5,18 366:12,13,16,19 367:1,2,9,21,22 weight-control 16:11 weighted 196:10,22 197:2 247:21 248:7,8,12 249:6,9,11 weight-related 28:11 weights 249:9 weight's 115:16 Weintraub 259:5 welcome 185:7	we'll 2:13 13:1,8 49:1 73:17,18 74:20 80:4 85:15 95:19 138:13 144:13 168:11 211:8 243:8 270:2,8 279:7 283:10 315:22 316:2 332:13,15 334:22 well-being 257:7 well-known 142:7 145:13 well-recognized 289:7 290:7 we're 11:11 52:18 55:10 56:10 59:1 75:10 76:20 77:14 78:3,5 83:19 88:20 89:13 90:9,10 104:1 115:3 121:4 124:7 126:19 130:3 133:8 139:1,3,17 146:20 150:21 157:15 171:21 173:2 174:16 185:20 186:3 211:6 243:21 248:11,12 257:21 269:12 275:6 318:6,20 321:6,15 324:5 326:15 328:17 329:22 330:2 332:10 341:21 342:1 345:15 346:8 348:5 351:1 356:12,15 359:3 360:8,18 365:3,19 366:12
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 93

we've 14:14 27:3 58:17 63:13 71:21 75:22 79:22 89:4,20 92:12 120:12 127:2 132:9 138:21 142:3,8 143:2,12,13 149:17 153:8 180:12,17 207:21 218:3 255:7,13 256:18,19,21,22 263:9 268:4 269:22 278:20 285:4 323:22 325:2 340:9 355:1 356:3 whatever 209:12 248:16 259:1 322:18 333:15,19 365:12,17 whereas 140:4 222:15,22 237:19 257:4 344:1 Whereupon 116:13 186:15 270:7 369:6 whether 22:13 51:4 55:10 57:19,21 63:17 64:14 65:15 66:7,19,20 67:13,19 68:9,19 101:14,15 104:3 106:5,10 107:22 113:13 139:14,16 143:6 151:12 173:2 174:15 180:16	185:21 203:20 205:21 225:4 237:16 241:18 242:7 249:11 256:3 259:1 279:1 282:11 328:22 332:9 333:12 334:22 335:5,19 343:17,18 353:16 358:3 360:10,12 361:6 362:10 365:1 white 1:12,15 28:7 123:10 152:22 208:4 299:14 Whitlock's 188:11 whole 85:16 123:6 133:15,20 152:14 181:17 201:16 214:20 261:7 316:10 whom 17:2 203:12,13 who's 106:1 110:8 111:19 172:9 whose 51:19 199:14 widely 296:13 widely-used 202:16 Willett 189:20 William 5:10 willing 173:6 175:20 261:9 345:4 window 238:2 Wing 13:13 116:21	144:14,15 168:9,11,14,21 170:15,18 171:2,15 172:14 173:1 174:13,22 175:5,8 177:7,11,15 179:20 180:7,10 181:13 182:4,7 183:22 184:12,19 185:2,4,18 192:9 194:2 200:20 255:4 342:4,11 343:10 345:1,9,14 347:2,6,12 349:7,9 350:12 351:12 352:19 353:13 354:5,20 357:3,14 366:6 367:20 368:14 wisdom 110:9 wisest 275:10 wish 172:20 withdraw 25:11,14 31:13 withdrawal 24:21 witness 9:1 Wolters 34:13 40:11 woman 52:10 142:5,10,13 women 43:5 52:13,15 64:9 66:22 68:4,9,11,14 78:9,12 91:12,13 100:11,14,20,22 139:13,20 140:4	148:17 155:17 188:14 189:22 284:4 318:12 319:8 Women's 4:12 91:9,15,21 wonder 24:6 100:16 106:15 172:5 244:20 258:17 328:22 wondered 107:5 163:6 185:14 342:21 343:8 wonderful 99:3 185:12 194:14 361:19 wondering 54:13 55:9 57:19 62:11 105:20 168:18 174:18 185:11,12 247:5,9 334:14 335:5,19 349:11 work 81:20 82:12 107:13 169:15 207:6 211:2 259:2 266:7 356:20 364:9 worked 86:22 117:8 124:6,18 257:8 337:5,12,13 working 15:2 71:15 77:14 90:2 138:19 151:9 152:10 184:2 218:16 works 207:6 world 24:17 262:16 263:14
---	---	---	---

Capital Reporting Company
Endocrinologic and Metabolic Drugs Advisory Committee 03-28-2012
Page 94

<p>worried 52:15 247:4 363:6</p> <p>worrisome 331:21 332:1 340:8,12,13</p> <p>worry 52:14 137:2 323:20,21</p> <p>worse 220:15 251:19 252:1</p> <p>worsens 290:10</p> <p>worth 213:17 222:10 236:10,15 242:11 326:21 328:13 363:5 366:5</p> <p>wound 344:21</p> <p>Wow 96:11</p> <p>wrestling 318:6</p> <p>write 260:9</p> <p>writing 9:3</p> <p>written 33:1,7 103:21</p> <p>wrong 50:13 264:11 332:3 336:21</p> <p>wrote 87:3</p> <hr/> <p style="text-align: center;">X</p> <hr/> <p>Xenical 24:9</p> <hr/> <p style="text-align: center;">Y</p> <hr/> <p>Yanovski 3:16 64:2,3 97:17,18 98:1 264:8,9 352:17,18 353:18 354:17</p> <p>Yanovski's 105:18</p>	<p>yellow 153:1 202:14 208:5 248:5 268:21 299:13</p> <p>yet 52:11 86:7 103:13,14 133:9 165:4 170:9 171:6 177:16 180:12 181:19 247:15 269:21 296:5 312:13 337:10 349:20</p> <p>yielding 315:12</p> <p>you'll 52:4 85:1 198:7 199:17 201:20 208:1 209:1 262:6 283:18</p> <p>young 88:12,15 89:7 141:15 142:9</p> <p>younger 46:16 132:18 156:21 157:7 335:13 360:15</p> <p>yourself 2:13 6:2 14:21 28:19 144:8 352:13</p> <p>yourselves 116:6 186:13 270:5 369:2</p> <p>you've 53:4 98:8 137:11 179:18 187:16 192:10 194:14 197:20 204:8 264:3 289:17 300:5 306:21 340:1 345:6 350:6 352:20 365:14</p>	<hr/> <p style="text-align: center;">Z</p> <hr/> <p>zero 40:19 247:14</p>	
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