

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

+ + + + +

70TH MEETING

+ + + + +

THURSDAY

MAY 14, 1998

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The Advisory Committee met in Versailles Rooms 1 and 2 in the Holiday Inn Bethesda at 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Robert Sherwin, M.D., Acting Chair, presiding.

PRESENT

- ROBERT S. SHERWIN, M.D. Acting Chair
- CATHY W. CRITCHLOW, Ph.D. Comm. Member
- JAIME A. DAVIDSON, M.D. Comm. Member

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1	JULES HIRSCH, M.D.	Comm. Member
2	ROGER D. ILLINGWORTH, M.D., Ph.D.	Comm. Member
3	ROBERT MARCUS, M.D.	Comm. Member
4	MARK E. MOLITCH, M.D.	Comm. Member
5	MARIA I. NEW, M.D.	Comm. Member
6	KATHLEEN R. REEDY	Exec. Secy.
7	LAWRENCE KATZNELSON	Guest Expert
8	PIPPA SIMPSON, Ph.D.	Consultant
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P R O C E E D I N G S

8:09 a.m.

1  
2  
3 CHAIRMAN SHERWIN: I think we can begin. I'd  
4 like to welcome you all here to our number 70 meeting  
5 of the Endocrine and Metabolic Drugs Advisory  
6 Committee. The drug that we will be discussing today  
7 is Ergocet™, preparation of bromocriptine by Ergo  
8 Science.

9 And we'd like to begin by introducing  
10 ourselves, and perhaps Dr. Sobel can begin on the  
11 right and we'll just go around the table.

12 DR. SOBEL: Sol Sobel, Food and Drug  
13 Administration, Metabolic and Endocrine Drugs.

14 DR. FLEMING: Alexander Fleming in the  
15 Division of Metabolic and Endocrine Drugs.

16 DR. PIAN: Lee Ping Pian, Division of  
17 Biometrics, FDA.

18 DR. DAVIDSON: Jaime Davidson,  
19 Endocrinologies in Dallas; member of the panel.

20 DR. SIMPSON: Pippa Simpson, Biostatistician  
21 at University of Arkansas Medical Sciences, Arkansas  
22 Children's Hospital.

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1 DR. MARCUS: Robert Marcus, Endocrinologist,  
2 Stanford University.

3 CHAIRMAN SHERWIN: Robert Sherwin,  
4 Endocrinologist, Yale School of Medicine.

5 MS. REEDY: Kathleen Reedy, Food and Drug  
6 Administration.

7 DR. MOLITCH: Mark Molitch, Endocrinologist,  
8 Northwestern University in Chicago.

9 DR. NEW: Maria New, Cornell Medical School,  
10 Pediatric Endocrinology.

11 DR. ILLINGWORTH: Roger Illingworth,  
12 Metabolism, Oregon Health Science University,  
13 Portland, Oregon.

14 MR. KATZNELSON: Larry Katznelson,  
15 Endocrinologist, Massachusetts General Hospital.

16 DR. CRITCHLOW: Cathy Critchlow, Department  
17 of Epidemiology, University of Washington, Seattle.

18 DR. HIRSCH: Jules Hirsch, Rockefeller  
19 University, New York.

20 CHAIRMAN SHERWIN: Okay. We will begin by  
21 having an open public forum, and I -- oh, excuse me,  
22 I'm sorry. I'm getting ahead of myself; I'm trying to

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1 move ahead.

2 We have a statement from Kathleen Reedy, our  
3 executive secretary, regarding conflicts.

4 MS. REEDY: The following announcement  
5 addresses the issue of conflict of interest with  
6 regard to this meeting and is made a part of the  
7 record to preclude even the appearance of such at this  
8 meeting.

9 Based on the submitted agenda for the  
10 meeting and all financial interests reported by the  
11 committee participants, it has been determined that  
12 all interests in firms regulated the Center for Drug  
13 Evaluation and Research which have been reported by  
14 the participants, present no potential for the  
15 appearance of a conflict of interest at this meeting  
16 with the following exceptions.

17 In accordance with 18 U.S.C. 208(b), full  
18 waivers have been granted to Drs. Mark Molitch, Robert  
19 Sherwin, and Jaime Davidson.

20 A copy of these waiver statements may be  
21 obtained by submitting a written request to the  
22 agency's Freedom of Information Office, Room 12A30 of

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1 the Parklawn Building.

2 In addition, we would like to disclose for  
3 the record that Dr. Jaime Davidson has interests which  
4 do not constitute a financial interest within the  
5 meeting of 18 U.S.C. 208(a) but which could create the  
6 appearance of a conflict.

7 The agency has determined not withstanding  
8 these involvements, that the interests of the  
9 government in Dr. Davidson's participation outweighs  
10 the concerns that the integrity of the agency's  
11 programs and operations may be questioned. Therefore,  
12 Dr. Davidson may participate in today's discussions.

13 In the event that the discussions involve  
14 any other products or firms not already on the agenda  
15 for which an FDA participant has a financial interest,  
16 the participants are aware of the need to exclude  
17 themselves from such involvement and their exclusion  
18 will be noted for the record.

19 With respect to all other participants, we  
20 ask in the interest of fairness, that they address any  
21 current or previous financial involvements with any  
22 firm whose products they may wish to comment upon.

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1 I will also define that in addition to the  
2 regular members of the Endocrinologic and Drugs  
3 Advisory Committee, Dr. Simpson is an SGE -- a special  
4 government employee consultant -- and has temporary  
5 voting status, and Dr. Larry Katznelson is a guest  
6 expert and does not vote.

7 CHAIRMAN SHERWIN: Okay. Thank you. the  
8 next step is to begin an open public hearing, and we  
9 have two statements to be read. The first is by  
10 Morgan Downey. If you could give your affiliation and  
11 how you ended up coming here in terms of expenses, and  
12 so on.

13 MR. DOWNEY: I will. Thank you, Mr.  
14 Chairman and members of the panel. My name is Morgan  
15 Downey. I am a person with obesity and I am executive  
16 director of the American Obesity Association. The AOA  
17 was founded in 1995 by Richard Atkinson and Judith  
18 Stern as an advocacy organization for the interests of  
19 millions of persons in this country with obesity.

20 The American Obesity Association is proud to  
21 have received support from major pharmaceutical  
22 companies including Hoffman LaRoche, Knoll

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1 Pharmaceutical, Medeva, American Home Products, Amgen  
2 and Interneuron.

3 In addition, AOA is supported by over 500  
4 dues paying individuals. It has not received any  
5 financial contribution from Ergo Science Corporation  
6 or Ortho-McNeil Pharmaceutical Corporation or Johnson  
7 & Johnson.

8 I appear before you today on behalf of the  
9 millions of obese persons with diabetes or at risk of  
10 developing diabetes.

11 According to the Centers for Disease Control  
12 and Prevention, 10.3 million Americans have been  
13 diagnosed with diabetes and another 5.4 million are  
14 thought to have the disease without knowing it.  
15 Approximately 90 to 95 percent of diabetes cases are  
16 of Type 2 which tends to develop after age 40.  
17 Obesity is a major risk factor for Type 2 diabetes.

18 The relation between average weight of a  
19 population and the prevalence of diabetes was  
20 established many years ago. The increased risk for  
21 diabetes has been reported to be about twofold in  
22 mildly obese persons, fivefold in moderately obese

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1 persons, and 10-fold in severely obese persons.

2 The duration of obesity is a more important  
3 determinant of the risk for development diabetes; a  
4 sobering fact when one considers the increase in  
5 childhood diabetes.

6 Obesity enhances insulin resistance. It has  
7 been shown repeatedly that weight reduction improves  
8 blood glucose control in diabetic subjects and that  
9 weight loss improves morbidity in diabetic persons.

10 Type 2 diabetes can sometimes be controlled  
11 by weight loss, exercise, and improved nutrition.  
12 According to the American Diabetes Association, 10 to  
13 20 percent of Type 2 patients are treated with diet  
14 and exercise, 30 to 40 percent with oral drugs, and 30  
15 to 40 with insulin or insulin and oral medications.

16 Survey findings report that one in three  
17 people with Type 2 diabetes feel discouraged about  
18 their ability to manage their disease. Not  
19 surprisingly, these feelings increase as the disease  
20 progresses and more patients move through the  
21 continuum of care.

22 Patients on insulin as compared to patients

1 using diet and exercise are less likely to feel they  
2 are winning the fight against diabetes and more likely  
3 to believe that their diabetes has interfered with  
4 their livelihood and confidence.

5 Obesity and diabetes present a deadly and  
6 costly combination. Direct medical and indirect  
7 expenditures attributable to diabetes were estimated  
8 at \$98 billion in 1997. Approximately 57 percent of  
9 the costs of non-insulin dependent diabetes are  
10 attributable to obesity.

11 The American Obesity Association trusts that  
12 this Advisory Committee will fully consider the safety  
13 and efficacy data on Ergocet™. We are encouraged by  
14 the report of studies indicating Ergocet™ has a  
15 clinically significant effect on both diabetic  
16 metabolism and cardiovascular risk.

17 Should this product be found to have an  
18 acceptable risk/benefit profile, we would hope that it  
19 would be promptly approved. Patients with obesity and  
20 diabetes need the hope and encouragement that comes  
21 from new products to treat their condition.

22 Thank you, Mr. Chairman.

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1 CHAIRMAN SHERWIN: Thank you. We next have  
2 a letter from the American Diabetes Association and  
3 that will be read by Kathleen Reedy.

4 MS. REEDY: From American Diabetes  
5 Association:

6 "We are writing on behalf of the American  
7 Diabetes Association to provide information to the  
8 Food and Drug Administration's Endocrinologic and  
9 Metabolic Drugs Advisory Committee which is meeting on  
10 May 14th, 1998, to review the safety and effectiveness  
11 of bromocriptine for the treatment of Type 2 diabetes.

12 "Bromocriptine represents a new class of  
13 diabetes oral medications believed to work by  
14 resetting metabolic activity that would improve  
15 glucose tolerance as well as reduce body weight.  
16 Obesity and glucose intolerance are significant  
17 factors in contributing to Type 2.

18 "There are currently estimated to be nearly  
19 15 million cases of Type 2 diabetes in the United  
20 States; about 9.3 million diagnosed and another 5.4  
21 million undiagnosed. Each year over 700,000 persons  
22 are diagnosed with Type 2 diabetes.

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1           "Type 2 diabetes is serious and insidious,  
2 often going undetected for seven to ten years, and all  
3 the while adversely affecting the microvascular and  
4 macrovascular system.

5           "Type 2 diabetes often develops in  
6 blindness, renal failure, amputation, stroke, and  
7 heart disease. Early detection and treatment of Type  
8 2 diabetes are critical to help reduce the  
9 complications of diabetes. Early intervention can  
10 also help lower healthcare costs attributed to  
11 diabetes which currently amounts to \$98 billion  
12 annually.

13           "The American Diabetes Association believes  
14 that pharmacological therapy for Type 2 diabetes is  
15 often an invaluable tool toward achieving improved  
16 metabolic control. Bromocriptine works to improve  
17 metabolic control by a mechanism very different from  
18 other agents currently available. In that regard it  
19 could broaden and enhance the diversity of treatment  
20 options available to clinicians.

21           "If the drug is shown to be safe and  
22 effective, we believe that its use will facilitate

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1 improved diabetes care, thereby reducing the enormous  
2 burden of diabetes.

3 "The American Diabetes Association applauds  
4 the scientific and medical research community and the  
5 FDA for the development, review, and clearance for  
6 marketing of new prescription medications that can  
7 safely and effectively treat Type 2 diabetes.

8 "While it is not the role of the Association  
9 to endorse individual pharmaceutical products, we do  
10 believe that safe and effective drugs as determined by  
11 FDA review, are important tools for healthcare  
12 professionals who treat people with diabetes.

13 "Sincerely, Stephen Satalino, Chair of the  
14 Board, Mayer Davidson, president, and Christine Beebe,  
15 president, Healthcare and Education, American Diabetes  
16 Association."

17 CHAIRMAN SHERWIN: Thank you. That's the  
18 end of our open hearing. Before we begin, Dr. Sobel  
19 do you have any remarks to make before we move ahead?

20 DR. SOBEL: I haven't prepared any, but no,  
21 I don't.

22 CHAIRMAN SHERWIN: Okay, thank you. Okay,

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1 we'll now begin with the presentation of Ergo Science.  
2 And the plan for today is, we will do our best to try  
3 to get through the presentation in an expeditious way.  
4 Hopefully, we can actually make it through to the  
5 break.

6 Now, if there are questions of key issues  
7 regarding the presentation, I would ask you to ask the  
8 questions of the speaker, but we would like to hold  
9 most of the discussion and the interchange after the  
10 presentation so we can spend the whole afternoon  
11 discussing the drug.

12 So try to keep your remarks to a minimum if  
13 at possible. Thank you.

14 DR. PAUL: I'm Richard Paul and I am with  
15 Ergo Science. I'm the senior vice president of  
16 Medical and Regulatory Affairs and I wish to amplify  
17 and extend my additional good morning to you, Dr.  
18 Sherwin, and your group, as well as to you, Drs.  
19 Fleming and Sobel and colleagues of the FDA.

20 I'd like to especially thank Michael  
21 Johnston for his assistance in the communications and  
22 in the things that go on between company and agency.

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1 He's done a remarkable job; I really wanted to point  
2 that out. Thank you, Michael.

3 We feel that it's important to at least  
4 identify the experts that we have brought with us  
5 today, which will be addressing different areas of  
6 interest as we discuss our product, Ergocet™, a new  
7 formulation of bromocriptine.

8 What I'd like to do is go through that. I  
9 will not give you each of their qualifications. I  
10 would be here until 5 o'clock this evening doing that.  
11 But I would just like to name them: Dr. Ralph  
12 DeFronzo, Dr. Arthur Rubenstein, Dr. Bertram Pitt, Dr.  
13 Barry Egg, Dr. Marcia Testa, Dr. George Steiner, and  
14 Dr. John Lachin. Welcome and thank you for joining us  
15 today.

16 Our charge here today is to do exactly this:  
17 to present to you the evidence -- driven by data,  
18 driven by the drug's history, the active ingredients  
19 -- that will support if you will, our claim platform  
20 which we are seeking, and what we're seeking to do is  
21 have Ergocet™, this new formulation of bromocriptine,  
22 be indicated for the treatment of Type 2 diabetes as

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1 an adjunct to sulfonylurea therapy, and both as  
2 monotherapy.

3 Ergocet™ we believe, offers in the milieu  
4 of oral hypoglycemic agents, a new approach, a central  
5 acting approach. We know that just recently there's  
6 been a plethora if you will, of new agents introduced  
7 into the armamentarium to treat Type 2 diabetes; most  
8 recently, repaglinide. We've had metformin, we've had  
9 precose, and others.

10 What's different about this approach is that  
11 we are actually getting into where the central switch  
12 is, if you will, for mediating most of what goes on  
13 around the end organs where most of the other agents  
14 act.

15 We do that by modulation of some key  
16 neurotransmitters in and around the hypothalamus in  
17 the brain; namely, dopamine, norepinephrine, and  
18 serotonin.

19 Again, we believe that the mechanism of  
20 action of this entry will be unique. It's new. We  
21 have shown their data and we will share with you this  
22 morning the facts and the evidence that we've been

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1 able to lower hemoglobin A1C, the surrogate for  
2 glycemic control. We've had an effect on both fasting  
3 and post-prandial glucose, triglycerides, and of free  
4 fatty acids.

5 We are once-a-day dosing, time dosing -- in  
6 the morning. Dr. Cincotta, when he delivers his  
7 address will tell you why we do that. And we have  
8 shown the product to be consistent with its history of  
9 being safe and well-tolerated.

10 I just thought I'd mention to you in the  
11 long road from 1991 when we filed the IND, going  
12 through each step of the way with the agency holding  
13 our hands -- on one side was the agency and on the  
14 other side was a group of very fine experts and we do  
15 recognize them.

16 Without further ado, because we do have a  
17 rather concrete and intense presentation to share with  
18 you this morning, I'd like to get right to that  
19 presentation. If you think of this as a story there  
20 are several chapters of the book to tell, and we're  
21 going to try to do that in a very stepwise fashion.

22 I would like, in the sake of saving time, to

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1 present the first two speakers this morning. Dr.  
2 Arthur Rubenstein is no stranger to any of us. He's  
3 been a pioneer in the field of diabetes. He is  
4 currently the executive vice president at Mt. Sinai  
5 Medical Center and is the academic dean of that  
6 institution's medical school.

7 Dr. Rubenstein has gained the respect, has  
8 earned several important awards, has been invited to  
9 sit on the peer review of several peer review  
10 journals. He's given countless presentations, has  
11 held high positions in the American Diabetes Center,  
12 and we're honored to have him here with us this  
13 morning.

14 Following a short presentation by Dr.  
15 Rubenstein, Anthony Cincotta, our executive director,  
16 our chief scientific officer, will then bring you  
17 through the first couple of chapters of the story --  
18 starting with the pre-clinical work that went on after  
19 identification of observations of animals in the wild;  
20 bringing you forward from that into the translational,  
21 clinical pharmacology research, proof of concept.

22 And then finally, sharing with us the

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1 further proof of the efficacy and safety of this drug.  
2 But Anthony will primarily focus on efficacy. I'll  
3 come back to tell you about the safety. And without  
4 further ado, Dr. Rubenstein, if you could come to the  
5 podium. Thank you.

6 DR. RUBENSTEIN: Thank you, Richard. Good  
7 morning everybody and I'm delighted to be here, and  
8 thank you for having me address you today in a short  
9 way.

10 I've been associated with Ergo Science for  
11 almost from the beginning, the last eight years. And  
12 one of the reasons was that I was always interested in  
13 the link that they showed between important, basic  
14 science and animal studies with the potential for  
15 treatment of diabetes.

16 At the time that I began the association  
17 with the company the treatment for diabetes -- Type 2  
18 diabetes -- was extremely limited. This has improved  
19 in the last few years and the development of this drug  
20 is one of several exciting advances that are important  
21 I think, for clinicians taking care of these patients.

22 It's in that context that I'm happy to be

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1 here today. My role is just to just highlight a few  
2 points, most of which are well-known to the panel.  
3 Some of which, too, have been made in an extremely  
4 good way by the public presentations, and so I will be  
5 short.

6 A couple of points though, are important.  
7 Diabetes is a very common disease -- and I'm focusing  
8 today on Type 2 diabetes -- involving a large number  
9 of our population. This is particularly a problem  
10 with the new ADA specifications which have a well-  
11 known rational and scientific basis in terms of the  
12 plasma glucoses which are now used for the diagnosis  
13 of this disease.

14 But this has enlarged the population with  
15 this disorder and made the importance for effective  
16 treatments even more persuasive.

17 As you know, this disease is most common in  
18 obesity, which is a big problem in our population; has  
19 a strong hereditary component; tends to be more common  
20 in women and in lower socio-economic groups; and all  
21 of these are important considerations in terms of an  
22 effective treatment to prevent the serious

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1 complications of the disease.

2 Now, the most important point which I think  
3 is well-known to you is the concept that has arisen  
4 after the DCCT trial -- the Diabetes Control and  
5 Complication Trial -- which of course involved Type 1  
6 diabetic patients, but which has given rise to the  
7 important concept that hypoglycemia is a key risk  
8 factor for the development of serious complications in  
9 diabetic patients.

10 And the underlying metabolic disorder of  
11 which hypoglycemia may be a surrogate, is keyly  
12 important in terms of microvascular disease -- the  
13 kidney, eyes, and nerves -- as well as macrovascular  
14 disease involving the coronary arteries, carotid  
15 arteries, peripheral vascular arteries, and so on.

16 There are numerous -- although not totally,  
17 not everyone accepts -- studies which seem to indicate  
18 that the same kind of relationship between a metabolic  
19 disturbance and complications, will exist in Type 2 or  
20 does exist in Type 2 diabetes.

21 And that of course, underlines a lot of the  
22 urgency to find effective and safe treatments that

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1 will lower the blood sugar towards or into the normal  
2 range.

3 A second point that I'd like to make in this  
4 regard is that in Type 2 diabetic patients, many of  
5 whom or most of whom are overweight, the hypoglycemia  
6 occurs in the setting of insulin-resistance; that is,  
7 a constellation of events including hypoglycemia,  
8 hyperlipidemia, hypertension, and a variety of other,  
9 well-known abnormalities. But those are the central  
10 ones.

11 And these are particularly important because  
12 that combination of metabolic abnormalities --  
13 particularly hypoglycemia, hyperlipidemia, and  
14 hypertension -- are particularly bad in terms of  
15 patient morbidity and mortality.

16 In that regard, the potential of Ergocet<sup>TM</sup>  
17 to both improve hyperlipidemia together with lowering  
18 the blood sugar, is an important advantage that should  
19 be carefully evaluated.

20 Now, these conclusions then indicate to me  
21 and fellow colleagues, I think clinicians, that  
22 aggressive treatment of Type 2 diabetic patients is

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1 appropriate and desirable, and we're left with the  
2 issue that we need a variety of safe and effective  
3 drugs to accomplish this.

4 And so in this context it's worth reviewing  
5 very briefly what is available for us. And I'll list  
6 them because they're well-known to you. I'll list  
7 them briefly.

8 The important, long-standing, oral  
9 hypoglycemic agents that are available to us are the  
10 sulfonylurea group, and more recently added to that,  
11 there are a variety of beta cell secretor guards which  
12 are related but not identical to sulfonylureas.

13 They work by enhancing, at least in the  
14 first instance, insulin secretion from beta cells, and  
15 they have been the stalwart of treatment of Type 2  
16 diabetes for many years.

17 The second category that was more recently  
18 introduced after a time when it was not on the market  
19 in the United States, are the bigonades -- metformin  
20 being the specific example -- and this drug, together  
21 with the sulfonylureas, did provide an important  
22 advance in terms of the treatment and control of

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1 hypoglycemia in a large number of Type 2 diabetes.

2 Other drugs have been introduced into the  
3 market with different mechanism of action in the last  
4 couple of years. The alphaglucoSIDase inhibitors  
5 which slow complex carbohydrate absorption by  
6 interfering with a breakdown in the gut to enzymatic  
7 inhibition, is another class of drugs that has been  
8 helpful.

9 And most recently the thiazolidine diones  
10 have been introduced which increase insulin  
11 sensitivity and have important molecular mechanisms  
12 that are being worked out in detail, and that  
13 interfere or enhance insulin action.

14 Of course, as was mentioned earlier, insulin  
15 itself can be used. Now, the point I'd like to make  
16 is, although this is an increasing and valuable  
17 armamentarium to treat the metabolic abnormalities in  
18 diabetes and hopefully prevent the complications,  
19 compared to many diseases like hypertension, coronary  
20 artery disease and so on, we still are somewhat  
21 limited in terms of producing the excellent final  
22 endpoint, which is normalization of the blood sugar

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1 and lipidemia that we know or feel would be highly  
2 desirable.

3 And it's in that context then that Ergocet™  
4 should be evaluated and has sparked the interest of  
5 several of us in terms of its potential. Richard  
6 mentioned that in terms of many unique findings --  
7 I'll summarize those finally in the end of my  
8 presentation -- the central mechanism of action is  
9 particularly intriguing because it is something  
10 totally different from any other drug that's on the  
11 market at this time.

12 And going all the way back to Claude Bernard  
13 and others, the potential of regulating metabolic  
14 effects through central mechanisms -- again, if it can  
15 be done effectively and safely, is extremely  
16 intriguing to me.

17 And through that mechanism it has a number  
18 of controlling metabolic effects which may be quite  
19 broad, such as control of hypoglycemia, perhaps  
20 through mechanisms of increasing insulin sensitivity  
21 that you'll hear presented today by my colleague,  
22 Ralph, control of lipid metabolism, particularly

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1 lowering free fatty acids and hypertriglycemia, which  
2 again is of importance as we discussed.

3 And the fact that it may have other effects  
4 which may affect obesity and so on, which are being  
5 investigated, is of great interest. The potential of  
6 the drug to be used alone or in combination then, with  
7 other hypoglycemic agents because of its unique,  
8 different mechanism of action again, is of interest.  
9 And its safety profile we believe, is excellent.

10 So in summary then, if one thinks of the  
11 development of drugs to treat this important disease,  
12 this drug potentially then has great interest and  
13 excitement because of many unique features that it  
14 has.

15 And in that regard I personally have watched  
16 this development with interest and it is actually  
17 gratifying that it has come this far that we can be  
18 presenting the material to you today.

19 Thank you. I don't know if there's any  
20 questions.

21 CHAIRMAN SHERWIN: Okay. We are good to our  
22 word so far.

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1 DR. CINCOTTA: Good morning to you all. I'd  
2 like to add my good morning to everyone else's. I am  
3 Anthony Cincotta and the chief science officer for  
4 Ergo Science.

5 This morning I'm going to be talking  
6 initially about the scientific rationale for the  
7 development of this drug, the treatment of Type 2  
8 diabetes, approximately 10 or 12 minutes, then I'll  
9 follow that with the transitional work -- essentially  
10 our proof of concept studies, our early Phase 2  
11 program -- at which point in time I'm going to turn it  
12 over to Ralph DeFronzo so he can demonstrate it --  
13 present his insulin clamp data.

14 There are several key points to keep in mind  
15 all through the presentations the entire day today,  
16 and they are the following. Number one, as you've  
17 heard from Dr. Rubenstein, we have a new target for  
18 intervention in Type 2 diabetes. It's virtually  
19 unique compared to all the other available agents.  
20 The target is centrally -- it's in the ventromedial  
21 portion of the hypothalamus in the brain.

22 We have found over studies of a variety of

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1 animal model systems, that abnormalities in  
2 norepinephrine and serotonin within the ventromedial  
3 hypothalamus significantly contribute to the  
4 pathophysiology of the diabetic state.

5 Bromocriptine, the active ingredient in  
6 Ergocet™, has the ability to reverse these  
7 abnormalities and thereby improve not only the  
8 glycemic control, but also dyslipidemia and insulin  
9 resistance as well.

10 Well, the central question right off the bat  
11 was, how did we come to the finding that the VMH is a  
12 potential target for drug therapy in the diabetic  
13 population? And the real answer to that question  
14 resides in the basic science that initiated the  
15 clinical development program for Ergocet™.

16 The basic science investigations were  
17 animals in the wild under natural conditions that  
18 exhibit annual cycles of the obese insulin resistant  
19 state.

20 This slide depicts one representative  
21 species from the wild, a Syrian hamster, that goes  
22 through a marked annual cycle of obesity and insulin

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1 resistance. And you can see that in the winter, in  
2 yellow, the animals are obese -- this is  
3 retroperitoneal fat pad weight on the left-hand panel.  
4 The center panel is plasma insulin level, and the  
5 right-hand panel is the plasma glucose level.

6 In winter the animals are obese and  
7 hyperinsulinemic. They're also insulin resistant.  
8 But as the springtime comes around the animals lose  
9 their obesity, they lose their hyperinsulinemia, and  
10 they become insulin sensitive.

11 All of this occurs without any change in  
12 food consumption, and the animals are not on any  
13 pharmacologic agent. So it was extremely intriguing  
14 to me, personally, when I started the research in this  
15 area, how are these animals doing this?

16 A more intriguing aspect was that it was not  
17 just the Syrian hamster. You could pick just about  
18 anything you wanted out of the wild and they still  
19 went through these marked annual cycles -- of  
20 metabolism independent of caloric consumption.

21 We therefore thought it wise to investigate  
22 this further to try and ascertain how this natural

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1 mechanism was occurring.

2 It was in fact -- this annual cycle that was  
3 providing a survival strategy, was not a genetic  
4 defect, okay -- and this is the second important point  
5 -- it was not a genetic defect. It's a survival  
6 strategy for these animals to survive long periods of  
7 low food availability.

8 And it was the hallmarks of that seasonal  
9 survival period that led us to the ventromedial  
10 hypothalamus. Because, on the next slide, the  
11 hallmarks of this seasonal obese condition are very  
12 similar to what you see in the obese, insulin-  
13 resistant, Type 2 diabetic human being.

14 Namely, they start out with  
15 hyperinsulinemia. This potentiates the obesity for  
16 these animals and they're using that fat. They become  
17 fat for a reason. They utilize it and utilized  
18 primarily in the muscle tissue of the body, sparing  
19 the glucose that is produced by the liver for the  
20 brain -- which has an absolute requirement for  
21 glucose.

22 There are long periods of the year -- three,

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1 four, five, six months at a time -- where there is no  
2 glucose available in the wild. They counter that by  
3 making their own glucose in the liver. They increase  
4 hepatic glucose production in part, by becoming  
5 insulin resistant -- shunt the glucose to the brain.

6 It's a very favorable, survival strategy.  
7 You could say actually, make the argument that if it  
8 were not for the ability to become obese and insulin  
9 resistant, evolution of the human species may have  
10 been dramatically altered.

11 These three areas of metabolic change are  
12 all initiated by the ventromedial hypothalamus, and  
13 that was really the clue that we should start looking  
14 in the brain. We know that it was a central mechanism  
15 because it was a timing system that was responsive to  
16 external stimuli, like changes in the photo period.

17 So we knew that it's centrally being  
18 regulated. Where in the CNS was really driven by the  
19 changes that were occurring metabolically in these  
20 animals. The ventromedial hypothalamus has the  
21 ability to influence all three of these parameters.

22 So we decided to look at the ventromedial

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1 hypothalamus in obese, insulin-resistant animals --  
2 both seasonal and non-seasonal -- with a variety of  
3 different model systems, and see what in fact were the  
4 neurochemical differences between the obese, insulin  
5 resistant, lean insulin-sensitive states.

6           And to do this we employed the technique  
7 called microdialysis, where actually dialyzing out the  
8 neurotransmitter in extracellular space in the  
9 ventromedial portion of the brain, over a 24-hour  
10 period while the animal is alive, conscious, feeding,  
11 sleeping, and going through their normal, locomotor  
12 activity rhythm.

13           Over a 24-hour period, on the X-axis here  
14 this depicts the dark portion of the day in yellow and  
15 this is the light portion of the day. And one can see  
16 when you do an HPLC analysis of these dialocytes from  
17 the ventromedial hypothalamus, the one thing -- and we  
18 measured everything that we could find in the VMH --  
19 the one thing that really jumped out at us was the  
20 change in the noradrenergic and serotonergic  
21 activities within the ventromedial hypothalamus.

22           The blue line represents the glucose

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1 intolerant animals in their glucose-intolerant state  
2 -- and they're also insulin resistant -- and you can  
3 see that noradrenergic activity is measured by  
4 extracellular metabolite of noradrenaline -- MHPG --  
5 and of serotonergic activity as measured by  
6 extracellular levels of 5-HAA, are increased in these  
7 insulin-resistant, glucose intolerant animals relative  
8 to the glucose-tolerant animals.

9 And this has occurred over and over again in  
10 a variety of different species. In fact, using a  
11 similar but different technique, other laboratories  
12 have published the same thing of other models of the  
13 obese, insulin-resistant state. So it's a very  
14 consistent finding amongst many laboratories now --  
15 elevated levels of noradrenaline and serotonin in the  
16 ventromedial hypothalamus.

17 This is an association at this point. We  
18 wanted to move to the next step -- a cause/effect  
19 relationship between these changes in the VMH and the  
20 change metabolism in the periphery.

21 And the way to do that most simply so that  
22 you can understand the results at the end of your

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1 experiment, is by starting out with a lean, insulin-  
2 sensitive, glucose-tolerant animal and infusing  
3 noradrenaline and serotonin into the VMH chronically  
4 so we can raise those levels up high, mimic the obese,  
5 insulin-resistant state, and see what metabolic  
6 changes ensue.

7 The next slide demonstrates the sequence of  
8 events that occur following initiation of this  
9 experimental paradigm. When you infuse -- when one  
10 infuses norepinephrine and serotonin into the  
11 ventromedial hypothalamus -- and we've done this in a  
12 couple of different species and the results are  
13 essentially identical among those different species  
14 that we tested -- we find that the earliest  
15 occurrences are increases in sympathetic tone  
16 peripherally; glucagon and cortisol secretion in the  
17 endocrine glands, and epinephrine secretion from the  
18 adrenal.

19 Concurrent with these increases there's also  
20 an increase in insulin secretion from the beta cells.  
21 We have created a very unique situation that already  
22 is starting to look like intermediary metabolism of

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1 the insulin-resistant state.

2 You have increased sympathetic tone,  
3 increased glucagon levels, but at the same time the  
4 animals are actually hyperinsulinemic, and this is  
5 following chronic infusion. That's not for a day or  
6 an hour; this is after a couple of weeks. It's still  
7 actually, a very short period of time considering  
8 we're starting out with a virtually normal animal.

9 The next sequence that follows is that the  
10 increases in the sympathetic tone, the glucagon and  
11 the epinephrine, strongly stimulate adipose tissue  
12 lipolysis. The free fatty acid levels begin to rise  
13 in the blood almost immediately and they stay elevated  
14 for a very extended period of time. In fact,  
15 continuously throughout the four or five week infusion  
16 period -- as long out as we've gone.

17 So you see an increase in lipolysis, the  
18 free fatty acid levels rise in the blood and the liver  
19 hepatic glucose production is increased substantially.  
20 These are again, two factors commonly associated with  
21 insulin resistance and the diabetic condition.

22 The elevated levels of free fatty acids that

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1        ensue from the lipolysis and increase the hepatic  
2        glucose output, in the face of hyperinsulinemia  
3        converge to all induce insulin resistance and  
4        ultimately, glucose intolerance.

5                The interesting thing here is that this  
6        whole sequence of events that occurs from this  
7        infusion of norepinephrine and serotonin in the VMH is  
8        not dependent on really any change in food consumption  
9        in these animals. The food consumption doesn't change  
10        dramatically over the time period of the infusion;  
11        secondly, their body weights don't change  
12        dramatically.

13                However, you end up with a severely insulin-  
14        resistant, severely glucose-intolerant animal at the  
15        end of this four or five week period. Also they're  
16        obese. Even though the body weight doesn't change,  
17        the body composition changes dramatically and the  
18        increase in the obesity further supports the increased  
19        lipolysis and the rise in the free fatty acid levels.

20                Ultimately these contribute to the diabetic  
21        condition. If in fact, increased norepinephrine and  
22        serotonin levels which are associated with this

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1 diabetic state in these animal models can be induced,  
2 the condition, it seemed it may be a very potent  
3 target site in that if we reduce these elevated levels  
4 we may see an improvement in peripheral metabolism as  
5 well as a consequence.

6 So how does bromocriptine fit into this  
7 picture? Bromocriptine is a unique neuromodulating  
8 agent. It has the ability to influence dopamine,  
9 serotonin, and noradrenaline simultaneously as a  
10 function of its neuromodulatory activities.

11 It's a D<sub>2</sub> agonist and thereby obviously  
12 increases dopamine activity at the D<sub>2</sub> site post-  
13 synaptically and pre-synaptically, but pre-  
14 synaptically it also reduces noradrenaline release and  
15 serotonin release.

16 As an alpha 1 antagonist it inhibits  
17 noradrenaline activities at the post-synaptic site.  
18 And it's also an alpha 2 agonist and reduces again,  
19 noradrenaline release by a second mechanism. And  
20 finally as a serotonin agonist, the pre-synaptic  
21 somatic dendritic portion of the neuron, it inhibits  
22 serotonin release.

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1           So you can see that through a variety of  
2 different receptor site activities, bromocriptine has  
3 a very potent activity of reducing noradrenaline and  
4 release in activities overall.

5           As it relates to the ventromedial  
6 hypothalamus, we did the next logical experiment.  
7 What happens if you give obese, insulin-resistant  
8 animals bromocriptine? And we looked into the  
9 ventromedial hypothalamus and see, did we influence  
10 norepinephrine and serotonin activities and if we did,  
11 how does that correlate with metabolic changes  
12 observed in the periphery?

13           The next slide demonstrates again, the  
14 results of these experiments. Now here we're using  
15 the exact same experimental paradigm -- this is 24  
16 hours of the day; the dark and light portions of the  
17 day.

18           This little arrow here represents the time  
19 of day that bromocriptine treatments were made daily  
20 to these Syrian hamsters, and we're measuring  
21 noradrenergic activity and serotonergic activity, here  
22 in the hamster, over the course of the day, before the

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1 treatment and then two weeks after the treatment.

2 And you can see that both noradrenergic and  
3 serotonergic activities that are elevated in these  
4 insulin-resistant, glucose-intolerant animals are  
5 reduced to levels that are observable in the insulin-  
6 sensitive animal.

7 So we've reduced the elevated noradrenergic,  
8 serotonergic activity that potentiates that insulin-  
9 resistance down to levels observed in the insulin  
10 sensitive, lean animal.

11 And in fact, what has correlated with this  
12 was an improvement in glucose intolerance, elevated  
13 free fatty acids -- right, where we're reducing that  
14 drive for lipolysis, the free fatty acid levels drop  
15 -- hypertriglyceridemia drops in large part because  
16 you're reducing the free fatty acids, and insulin  
17 resistance is also reduced substantially -- actually  
18 normalized compared to the seasonal, lean animal.

19 An important point to remember is that that  
20 bromocriptine treatment that induced these changes in  
21 the ventromedial hypothalamus and subsequent  
22 improvement in all these metabolic parameters

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1 peripherally, maximally induced -- if it's injected at  
2 the appropriate time of day -- we made those  
3 injections of bromocriptine late in the afternoon as  
4 opposed to early in the morning.

5 We did not see a drop in noradrenaline and  
6 serotonergic activity in the ventromedial  
7 hypothalamus, or we did not see any major improvement  
8 in any of these metabolic activities in the periphery  
9 -- the time-of-day dependent responsiveness in this  
10 system to the dopamine agonist.

11 Then to review, the neuroendocrine  
12 abnormalities induced in this insulin-resistance  
13 glucose-intolerant state is it presents itself  
14 naturally in animals and the wild, and with a variety  
15 of other man-made diabetic animal model systems is the  
16 following.

17 Increases in noradrenergic  
18 serotonindrenergic tone, in the VMH potentiate  
19 sympathetic tone glucagon norepinephrine secretion  
20 simultaneously with insulation -- it's not shown here  
21 -- would potentiate increased adipose tissue lipolysis  
22 very strongly, resulting in increased serum free fatty

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1 acid levels, in VLDL triglycerides.

2 They also potentiate increases in hepatic  
3 glucose output from the liver, obviously. Together  
4 these stimulate or potentiate the induction and the  
5 maintenance of insulin resistance both in the liver  
6 and in the muscle tissues.

7 There is a second mechanism independent of  
8 adipose lipolysis by which this norapys serotonin in the  
9 VMH can actually induce insulin resistance in the  
10 muscle tissue.

11 We're not going to go over that now.  
12 Suffice it to say that this is not the only mechanism  
13 by which is -- the majority of the situation.  
14 However, there is another independent pathway here  
15 that we're actually working out in the laboratory  
16 right now. The bottom line is, this is the culprit  
17 all of the time, in all the animal species that we've  
18 investigated.

19 So it seemed reasonable to try and  
20 ameliorate the situation with the bromocriptine and to  
21 review the effects of bromocriptine on the situation.  
22 Where is bromocriptine working to improve glucose

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1 intolerance and dyslipidemia in these animal models?  
2 It's up at the top, at the initiation site.

3 That is one that essentially appears to be  
4 commonly present in animals in the wild. This evolves  
5 over eons, if not millions of years of time.

6 Bromocriptine reduces this noradrenergic and  
7 serotonergic drive, therefore reducing its VMH drive  
8 for noradrenergic activities and sympathetic tone and  
9 hyperinsulinemia; thereby reducing lipolysis and  
10 hepatic glucose output in the periphery; thereby  
11 reducing insulin-resistance and glucose intolerance in  
12 the animal organismal level.

13 And also it blocks this positive feedback  
14 loop insulin resistance has to maintain high levels of  
15 norepinephrine and serotonin in the VMH.

16 So to conclude, my adult's life work, the  
17 work in this area on one slide, the abnormal  
18 ventromedial hypothalamic activity significantly  
19 contribute to the insulin-resistant glucose-intolerant  
20 state.

21 But more specifically, it's that increased  
22 noradrenergic and serotonergic drive within the VMH --

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1 it's not a neuropeptide, it's not dopamine -- it's  
2 noradrenaline and serotonin and they're working  
3 synergistically to induce that insulin-resistant  
4 state.

5 Bromocriptine corrects those abnormalities  
6 at the top and thereby improves at the same time,  
7 simultaneously, hyperglycemia, hypertriglyceridemia,  
8 the elevated free fatty acids and insulin-resistance  
9 that are all ensued by that VMH neurochemistry.

10 Okay, without any further ado I'm just going  
11 to pass right now into our early, clinical  
12 pharmacology section. How do we take this information  
13 that we obtained from these animal model systems and  
14 try to apply it to the human situation?

15 Our early clinical development program  
16 essentially served two functions for us: one was to  
17 demonstrate the proof of concept in man, of this  
18 particular approach to treat the obese, insulin-  
19 resistant, diabetic condition, and at the same time --  
20 at least Phase 2 studies served to facilitate the  
21 appropriate design for our pivotal Phase 3 studies.

22 There are simple, four objectives here in

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1 our early clinical development program. One was, we  
2 wanted to assess the appropriate dosing time. If you  
3 remember I mentioned that all those effects of  
4 bromocriptine in those animal model systems were time-  
5 of-day dependent. We had to figure out, well what's  
6 the best time of day to give the drug to get the  
7 maximal effect in the human?

8 Secondly, the classic pharmacology studies;  
9 we wanted to assess a threshold dosage for the drug  
10 and look at the effects over a 24-week treatment  
11 period since that would be the experimental design  
12 we'd be employing in our Phase 3 studies.

13 And then finally, identify in some sort of  
14 reasonable way, the most favorable dose by therapeutic  
15 index.

16 Okay, let's just move right to the timing  
17 rationale. How do we pick the right time to give this  
18 drug in these humans? In our animal studies we again  
19 noted, that it was a centrally mediated effect. It  
20 was central dopaminergic tone that we are raising up  
21 to reduce that noradrenergic and serotonergic  
22 activity.

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1           And the effects were time-of-day dependent;  
2           that response to the dopamine agonist time-of-day  
3           dependent. How do we pick the right time of day? It  
4           was easy to pick it in the animals because we could  
5           measure what was going on in their brains. There are  
6           no non-invasive methods for doing that in humans so we  
7           had to find some respectable, accurate, reasonable,  
8           surrogate marker in the periphery.

9           And our choice was the serum prolactin level  
10          as a possible surrogate marker for central  
11          dopaminergic tone. This isn't the best method of  
12          doing this but at the point in time that we ran these  
13          studies it was all there was available to us, and it  
14          turned out to be, I believe, quite appropriate.

15          The key point is that in the diabetics as  
16          you'll see in the next slide, the daytime levels of  
17          prolactin are elevated in the diabetic population  
18          versus the non-diabetic population. And we used that  
19          time of day when there was this elevation in prolactin  
20          to represent a time of decreased dopaminergic tone and  
21          that's where we gave the dopamine agonist.

22          The next slide represents the result of one

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1 of several of those studies. And just to run through  
2 this quickly for you. The X-axis is the time of day.  
3 It's a 24-hour period. And on the Y-axis we have  
4 plasma prolactin levels. You can see that in yellow,  
5 the diabetic males, prolactin levels over the day are  
6 elevated relative to -- these are historical male  
7 controls from the literature -- they're representative  
8 of several studies.

9 Again, you can see that there's no  
10 difference in the nocturnal levels of prolactin  
11 between the two groups. It's really only during the  
12 daytime. And level changes here don't represent  
13 hyperprolactinemia in the classic clinical sense, but  
14 they are nonetheless, at least two or sometimes three-  
15 fold higher than they are in the non-diabetic.

16 And we took this discrepancy, this  
17 difference, to suggest that the reason these levels  
18 were higher is because there was decreased  
19 dopaminergic tone at this time of day. We wanted to  
20 give our dopamine agonists to increase that  
21 dopaminergic tone, here, in the early morning hours of  
22 the day.

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1           In other words, this is just representing to  
2 us what's happening centrally. Here's the decreased  
3 dopaminergic tone. By the way, these results have  
4 been reproduced by several other laboratories.  
5 Everyone that runs these studies essentially sees a  
6 very similar pattern for the most part.

7           Elevated diurnal prolactins; no change in  
8 the nocturnal situation. So we timed the  
9 bromocriptine or the Ergocet™ to the early morning.  
10 The next slide goes over the next aspect of this Phase  
11 2 study program looking at the threshold dose  
12 rationale.

13           Again, the target is the central nervous  
14 system D<sub>2</sub> receptor sites. But in this case we used  
15 prolactin in a different way than I just described for  
16 a marker for dopaminergic tone. We're using it as a  
17 marker for responsiveness -- level of responsiveness  
18 to our dopamine agonist.

19           The story goes like this, basically. The  
20 ED50 for prolactin inhibition with bromocriptine or  
21 the amounts of bromocriptine that's needed to inhibit  
22 prolactin secretion, is much less than what's needed

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1 to stimulate central D<sub>2</sub> receptors in that VMH region  
2 of the hypothalamus.

3 Therefore, if the dose is not strong enough  
4 or large enough to reduce prolactin, you're probably  
5 not stimulating the D<sub>2</sub> receptor sites which are the  
6 target. This is what we want to do to improve  
7 glycemic control.

8 Therefore, the threshold dose for efficacy  
9 should at least reduce your diurnal prolactin levels  
10 in those diabetics that are elevated, okay? So  
11 essentially, they're just associations that we are  
12 making that turned out to hold up pretty well.

13 The next slide shows a clinical trial design  
14 to test out our threshold dose of Ergocet™ used in  
15 our very earliest studies. These are obese, Type 2  
16 diabetics, randomized to 1.6 milligrams. These are  
17 0.8 milligram tablets of Ergocet™ that we  
18 manufactured and are using in our clinical trials --  
19 1.6 milligrams per day and we treated the people for  
20 approximately -- exactly 12 weeks.

21 The primary efficacy was total glycated  
22 hemoglobin change from the baseline. We had done some

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1 studies where we looked at the effect of .8 to 1.6 on  
2 reducing prolactin. We found that 1.6 was  
3 approximately a threshold dose for reducing those  
4 diurnal prolactin levels, and that's why we chose that  
5 in this particular study.

6 The next slide reviews the effects observed  
7 in this short, 12-week treatment period. You see this  
8 is decreased from the baseline. In the total glycated  
9 hemoglobin the Ergocet™ does improve glycemic control  
10 in the study. There's a reduction of about 0.7 for  
11 the all-Ergocet™ group relative to the placebo. It's  
12 statistically significant. This is after 12 weeks of  
13 treatment. Very happy to find this very early on.

14 Well, on closer inspection of the data, the  
15 next slide shows that for those individuals on  
16 Ergocet™ where the prolactin levels were normalized  
17 during the diurnal portion of the day, they were  
18 reduced to normal. We thought a very good effect  
19 relative to the placebo.

20 However, for that subset of Ergocet™  
21 subjects where the dosage of 1.6 milligrams was not  
22 strong enough to reduce the prolactin, we did not see

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1 any improvement in glycemic control. Again, fitting  
2 with the hypothesis and the pharmacologic data showing  
3 that if the dosage is not strong enough to reduce the  
4 prolactin we can't activate those D<sub>2</sub> receptors  
5 centrally.

6 So we took this information to suggest, yes,  
7 1.6 milligrams is around the threshold dose because it  
8 will work in some 43 percent of the subjects, but in  
9 the majority, in 57 percent, it's not strong enough to  
10 reduce -- the prolactin level must not be strong  
11 enough to activate D<sub>2</sub> receptors. You should not see  
12 an effect and you don't see an effect.

13 Then we took this information, moved on to  
14 our next Phase 2 study which is a little bit larger  
15 and numbers were somewhat larger than the previous  
16 study, and we employed a larger dosage -- 3.2  
17 milligrams of Ergocet™ per day.

18 And now we are getting to a dosage where  
19 you're normalizing the prolactin and theoretically  
20 activating D<sub>2</sub> receptors in the majority of the  
21 patients; not 43 percent but now closer to 100  
22 percent.

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1           And the treatment period here was for 24  
2 weeks. It was a double-blind placebo-controlled  
3 study. Again, the primary efficacy variable that we  
4 were assessing was HbA1c change from the baseline  
5 after the 24-week treatment period.

6           The next slide demonstrates the results of  
7 that study. These were individuals on an isocaloric  
8 diet and these are the data from the isocaloric arm of  
9 the study. You can see the change again, from the  
10 baseline in the HbA1c.

11           There's no change -- I'm sorry, there was an  
12 increase from the baseline from approximately 0.7  
13 HbA1c, versus no change from the baseline for the  
14 Ergocet™ group. And the P value did not reach  
15 statistical significance -- it was .1.

16           However, when we looked at the subset of  
17 this population that was in fact, weight-maintained --  
18 defined as maintaining their body weight within two  
19 percent of their initial body weight; in other words  
20 they weren't gaining weight during the study -- we see  
21 that that difference between the placebo and the  
22 Ergocet™ group is somewhat larger and now does reach

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1 statistical significance at the .01 level.

2 We took this information, again, to employ  
3 the development and the design of our Phase 3 studies.  
4 The next series of studies were really aimed at  
5 finding that optimal therapeutic index.

6 We knew that around 3.2, somewhere in that  
7 range, we were getting an efficacy result, but we did  
8 a small dose ranging study of short duration where we  
9 took all these Type 2 diabetics and randomized them to  
10 treatment with one of several different doses of  
11 Ergocet™ from zero milligrams per day in the placebo  
12 group, all the way up to 15.2 milligrams per day.

13 It was a 35-day treatment period so we were  
14 not using HbA1c as our efficacy variable here because  
15 of the short period of time. Instead we took blood  
16 samples from these individuals beginning and end of  
17 treatment around the clock, approximately every other  
18 hour over the 24-hour period, and we measured the  
19 change in the area under the glucose curve as an  
20 indicator of an improvement in glycemic control over  
21 the 35-day treatment period.

22 The next slide demonstrates the results of

1 those studies. On the X-axis we have the dose of  
2 Ergocet™ from zero milligrams per day, here, all the  
3 way out to 15 milligrams per day, here.

4 On the Y-axis again, is the change from  
5 baseline in the area under the curve. The greater the  
6 decrease in the area under the curve from beginning to  
7 end, obviously the greater the improvement in glyce-  
8 mic control.

9 So as these numbers go down that means the  
10 glyce- mic control is improving more and more. And you  
11 can see that generally speaking, as you increase the  
12 dosage from zero all the way down, out to 15  
13 milligrams per day, there is an improvement in  
14 glyce- mic control. It's fairly linear.

15 Then how do we pick the appropriate dose to  
16 use in our Phase 3 studies? Well, associated with an  
17 improvement in glyce- mic control with this drug there  
18 is also, as we increase the dosages up to the 4.8  
19 milligrams per day dosage, you see that there is a  
20 very obvious increase in the incidence of mechanism-  
21 related -- these are D<sub>2</sub> receptor mechanism-related  
22 signs and symptoms.

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1           On the Y-axis again, we have reporting the  
2 percent of the subjects reporting symptoms. On the X-  
3 axis again, is the dose. And you can see that as the  
4 dosage increases your signs and symptoms increase but  
5 there's a very definite break when we move from 4.8 to  
6 7.2 milligrams per day.

7           One point here, as we look at the actual  
8 numbers of signs and symptoms, this was using a very  
9 fast titration -- .8 milligrams every three days -- so  
10 that they were titrated up to the final dose in two  
11 weeks.

12           In our Phase 3 studies we employed a much  
13 slower titration rate, up so that they reached the 4.8  
14 milligram dose over six weeks, and the overall  
15 incidence rate of all signs and symptoms are greatly  
16 reduced.

17           Nonetheless, the point is that at dosages  
18 above the 4.8 milligram dosage you see a very marked  
19 increase in signs and symptoms related to D<sub>2</sub> agonist  
20 activities. We therefore picked the most optimal dose  
21 as 4.8 milligram, because it gave the most efficacy  
22 with the least signs and symptoms related to the

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1 mechanism of D<sub>2</sub> agonist.

2 The next slide, in conclusion from these  
3 Phase 2 studies, we were going to employ a once-a-day  
4 administration just as we did in our animal model  
5 systems; that administration was going to be in the  
6 morning. It was timed there based on data obtained  
7 from elevated prolactins over the diurnal as opposed  
8 to the nocturnal portion of the day.

9 The drug did improve glyceic control over  
10 the 24-week treatment period, especially in the  
11 weight-maintained subjects. And the most favorable  
12 therapeutic index from all of our studies, turned in  
13 our minds to be 4.8 milligrams per day.

14 With that, at this point I'd like to turn  
15 the discussion over to Dr. Ralph DeFronzo who will  
16 discuss his own particular data with this drug in  
17 terms of insulin sensitivity and its ability to  
18 improve insulin sensitivity in the human being and  
19 correlate it with essentially what we had discussed in  
20 the animal model systems. Ralph?

21 CHAIRMAN SHERWIN: Before we go to Ralph I  
22 think there's -- Jules, do you have a question?

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1 DR. HIRSCH: I just had a clarification.  
2 I'm not sure I understood in terms of the model of  
3 this. Did you say that animals that have seasonal  
4 changes in body weight -- which is a common thing  
5 migratory birds -- that they do not have hypofagia?  
6 Is that what I understood you to say?

7 DR. CINCOTTA: Yes. It's a common  
8 misconception. If you go to the zoological literature  
9 and you look at all the studies that have been done --  
10 and these go back a long time with a lot of different  
11 species -- the point that jumps out at you is that you  
12 cannot explain all of the increase in obesity that  
13 occurs seasonally as a result of increased food  
14 consumption.

15 In fact, in many species -- and we could  
16 list several of them here; a great one for this part  
17 of the country would be the white-tailed deer --  
18 there's increases in body fat stores that are not  
19 associated with increased food consumption.

20 And what essentially is happening is there's  
21 a shift in body composition. The calories that are  
22 taken in are shifted towards increased body fat stores

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1 and away from protein turnover. So that the body  
2 weights on these animals may not change, but their  
3 lean to fat mass ratio changes substantially.

4 It does not require a change in food  
5 consumption. Obviously in these instances there is a  
6 change in energy expenditure and that's where  
7 bromocriptine is working. I mean, it's a good drug  
8 but it's not powerful enough to break the laws of  
9 thermodynamics.

10 Essentially what's happening is, these  
11 animals are going through their annual cycle and  
12 they're putting on the body weight but do not  
13 necessarily have to increase food consumption. If you  
14 bring them into the laboratory and you feed them the  
15 exact same calories all year long, they still go  
16 through their annual cycle with actual marked  
17 precision.

18 So it is not the driving force -- it is not  
19 the driving force for the obesity.

20 CHAIRMAN SHERWIN: Dr. Molitch? I have a  
21 feeling we're going to have a few questions but I  
22 would like to limit them because there's a lot of data

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1 that I'm sure we'll need to discuss subsequently, and  
2 it probably is not the best time. But Mark, would you  
3 like to make a comment?

4 DR. MOLITCH: Yes. The translation of the  
5 animal model to the human model seems to rest on the  
6 study that you showed on the elevated daytime blood  
7 sugars in the diabetic subjects compared to the  
8 controls. And I noticed that you said that these were  
9 historical controls.

10 I'd like to hear more about the subjects,  
11 the historical controls. Were they one and the same  
12 assay? Where did these controls come from? I want to  
13 know the ends, I'd like to know the weights and the  
14 ages in both of these groups.

15 DR. CINCOTTA: The historical controls used  
16 were age-matched. They were not weight-matched  
17 because we were comparing obese Type 2 diabetics to  
18 lean, insulin-sensitive subjects.

19 Actually, the differences that we do see in  
20 the diurnal portion of the day in the prolactins  
21 relate also to the obesity, and probably more  
22 specifically to obese insulin-resistant condition

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1 because if one looks in the literature where they've  
2 got the appropriate controls in their studies, they  
3 report the exact same responses that we're seeing.

4 In other words, it's not a function of the  
5 diabetes itself per se, but possibly more a function  
6 of just the obese insulin-resistant state, because the  
7 data in the literatures where they do have their  
8 matched controls with the same assay system, with the  
9 same individuals, they do see essentially the same  
10 differences. And it's been reported by several labs.

11 DR. MOLITCH: I'm really referring to this  
12 specific study, that's why I asked the question now  
13 about the specifics of that rather than the  
14 generalities of the literature which we could talk  
15 about later.

16 So I would really like to know in the  
17 diabetic population that you had, did they look for  
18 insulin resistance, what were the body weights, and  
19 what was the number of subjects, and also the controls  
20 -- were those prolactins run in the same assays or are  
21 they different assays, and how many controls were  
22 there?

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1 DR. CINCOTTA: The n number for the  
2 experimental group on that particular slide was  
3 approximately 20; for the historical control it was  
4 approximately ten. They are age-matched; however,  
5 they are different body weights. The BMIs for the  
6 individuals in the obese group was approximately 32.  
7 And it was -- for the lean group, if I'm not mistaken,  
8 was approximately 23.

9 DR. MARCUS: I'm troubled by this same  
10 issue. Mark asked most of my questions but I need  
11 reassurance that you have simultaneous running in the  
12 same assay, samples from controls and from Type 2  
13 obese diabetics; that this is not a comparison of  
14 literature-published values with your independently  
15 determined prolactin levels in a different assay.

16 DR. CINCOTTA: Actually, we don't have those  
17 data to show you today, but again, from the literature  
18 where they have done exactly what you're suggesting,  
19 the patterns are the same.

20 DR. MARCUS: That experiment has been done  
21 and diabetics show consistently, higher prolactin  
22 concentrations during the day than simultaneous

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1 controls recruited in the same assay in the same  
2 study, treated in the same identical manner in a CRC  
3 or some other facility.

4 DR. CINCOTTA: Yes. I might also add that  
5 above and beyond that, there are several papers in the  
6 literature showing hyperprolactinemia -- now we're  
7 talking about a more elevated situation here -- but  
8 hyperprolactinemia being associated with insulin  
9 resistance, hyperinsulinemia within obesity --

10 DR. MARCUS: I understand that but  
11 generally, my recollection of many of those papers is  
12 that they're based on a single, fasting plasma  
13 specimen or a random specimen, not trying to show the  
14 diurant curves which is at least, if not the rationale  
15 for the treatment it certainly is the rationale for  
16 the mechanism that you're attributing to the effect of  
17 the treatment.

18 DR. CINCOTTA: It's not the rationale for  
19 the mechanism. Remember the mechanism relates  
20 centrally. We're just using that prolactin only --

21 DR. MARCUS: As a surrogate marker. I --

22 DR. CINCOTTA: -- as a surrogate marker, and

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1 it's really even more minimal than that. We're using  
2 it as a surrogate marker only for the minimum  
3 effective dose of the drug, or the threshold dosage of  
4 efficacy.

5 And this was early on in our Phase 2  
6 development program, so the weight and the emphasis on  
7 that particular aspect of it was really not that  
8 great. We were just really trying to make whatever  
9 correlations honestly, that we could at that point in  
10 time.

11 DR. KATZNELSON: One more question for you,  
12 please. I'm not going to belabor this -- I know we'll  
13 discuss this further -- go back to the prolactin issue  
14 again.

15 It's key here, your issue about diurnal  
16 rhythms, and I agree with Dr. Marcus and Molitch what  
17 they said about this in fact. We recently published  
18 a paper showing prolactin levels in normal men  
19 reaching levels that were close to or if not  
20 overlapping, what you claim are obesity levels. We  
21 can discuss this more later.

22 My question for you also, in addition to the

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1 question of whether assays were similar, did you  
2 measure other factors that may regulate prolactin --  
3 estradiol, antigens? Do you know anything else about  
4 these patients? Which may be altered in obesity?

5 DR. CINCOTTA: Right. These -- well, to get  
6 at -- you're probably getting at the hypogonadal  
7 situation, maybe?

8 DR. KATZNELSON: Yes.

9 DR. CINCOTTA: Yes, they were not  
10 hypogonadal.

11 DR. KATZNELSON: But did you measure  
12 peripheral estrogen levels?

13 DR. CINCOTTA: No, we did not.

14 CHAIRMAN SHERWIN: Dr. Molitch. Hopefully,  
15 we can keep it short.

16 DR. MOLITCH: Again, just specifics related  
17 to these studies that you talked about -- the official  
18 dose study and the study G. Were the weight changes  
19 in the responders -- the Study A where you had 43  
20 percent of patients that were responders -- what were  
21 the weight changes that occurred in those individuals  
22 compared to the non-responders?

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1 DR. CINCOTTA: There are no differences in  
2 the weight change.

3 DR. MOLITCH: Okay. and in your dose ranging  
4 study that you had, where you saw the hemoglobin A1c  
5 versus dose very nicely, what was the correlation with  
6 prolactin levels?

7 DR. CINCOTTA: As you increase the dosage  
8 the very end of the 24-hour prolactin curve also  
9 decreases linearly.

10 DR. MOLITCH: And was there a relationship  
11 with the hemoglobin A1c change as an independent  
12 factor of that?

13 DR. CINCOTTA: No, only at that threshold  
14 dosage.

15 CHAIRMAN SHERWIN: Okay. I think what we'll  
16 do is move on, and we're going to re- I think, explore  
17 these issues later on in terms of the basic  
18 fundamental mechanisms. But I think it's time to get  
19 to the clinical presentation by Dr. DeFronzo.

20 Now Ralph, before you begin, there was  
21 something mentioned about clamp studies, is that  
22 right?

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1 DR. DeFRONZO: I'm going to primarily review  
2 a small study to look at insulin sensitivity. In this  
3 study there are data of course, on glycemc control.

4 CHAIRMAN SHERWIN: No, but clamps.

5 DR. DeFRONZO: Clamps.

6 CHAIRMAN SHERWIN: The reason is that I  
7 would appreciate it if you'd be very slow, and the  
8 reason is, we've not seen any of this data, to my  
9 knowledge. At least I -- it wasn't in our material.  
10 And so that is a concern for us, I think, because  
11 we're going to need to carefully see the data up there  
12 because we haven't -- and we would like to see copies,  
13 I think --

14 DR. DeFRONZO: Sure.

15 CHAIRMAN SHERWIN: -- of the slides so that  
16 we can have a chance to review it at lunchtime.

17 DR. DeFRONZO: I think Bob is familiar with  
18 my speech pattern which tends to go rather rapidly.  
19 But it's been slowed by the fact that my core body  
20 temperature is about 85 degrees now.

21 DR. SHERWIN: Incredibly, we actually  
22 recognize the problem.

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1 DR. DeFRONZO: You have maximally stimulated  
2 the hypothalamic function and shivering thermogenesis  
3 is at a maximum here. So if I'm stuttering it's  
4 because my whole body is shivering. It would be nice  
5 if we could --

6 CHAIRMAN SHERWIN: We've already got it.  
7 We're already working on it, Ralph.

8 DR. DeFRONZO: Actually, my dose of T4 was  
9 being underreplaced. If we could have the first slide  
10 -- or maybe I can make it go from here.

11 The purpose of the study that I'm going to  
12 review with you today was to look at the effect of  
13 dopamine, and you've already heard that this is a  
14 sympatholytic D<sub>2</sub> agonist. And the purpose is to look  
15 at the effect here on glucose tolerance insulin  
16 secretion and insulin sensitivity of obese, Type 2  
17 diabetic patients.

18 The experimental design is as depicted here.  
19 This is a double-blind, placebo-controlled study. The  
20 randomization was two to bromocriptine, one for the  
21 placebo group. There are 15 in the bromocriptine,  
22 seven in the placebo group.

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1           People were started on .8 milligrams per day  
2 of bromocriptine. The dose was increased by this  
3 increment every week up to a maximum of 4.8 by week 6,  
4 and there were a variety of studies which were  
5 repeated before and at the end of the study, which  
6 lasted for four months.

7           Now, an important part of the study was that  
8 the patients met with the dietician every one to two  
9 weeks to ensure constancy of body weight. If the  
10 weight was stable they met every two weeks. Sometimes  
11 if we saw that the weight was changing they would meet  
12 the dietician more frequently to review their diet,  
13 because we wanted to ensure that any findings were not  
14 going to be related to changes in body weight.

15           A control group is shown here in pink. The  
16 diabetics were randomized; received either  
17 bromocriptine, orange, or placebo in yellow. The  
18 gender distribution was not significantly different  
19 amongst the three groups. The age again, was similar  
20 between the three groups.

21           Eight of the bromocriptine patients who were  
22 on sulfonylureas; six on placebo. The mean duration

1 of diabetes was 3.2 and about 3.5 years in the  
2 placebo. Starting body weights which are shown here  
3 in the three groups did not change following therapy,  
4 nor did the BMI.

5 We measured fat in a number of ways.  
6 Underwater weighing are the data that I'm going to  
7 show to you. The percent fat is shown here.  
8 Obviously these people are significantly overweight  
9 because of an increase in fat mass, but at the end of  
10 the study there were no significant changes in fat  
11 mass.

12 Now, these are the studies that were  
13 performed before and at the end of the study period.  
14 Each subject had an oral glucose tolerance test. It  
15 lasted two hours and during the OGT we measured of  
16 course, the glucose; we measured the insulin levels;  
17 and we also measured of course, before and at the end  
18 of the study, the hemoglobin A1c.

19 Subjects had a 2-step euglycemic insulin  
20 clamp. Those of you who are not familiar with this,  
21 what we do is that we raise the insulin by a fixed  
22 amount, maintain the blood sugar level constant, and

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1 we let it drop down to 90 milligram per deciliter so  
2 they were all clamped at euglycemic levels.

3 And then the studies are carried out with  
4 tritiated glucose from which we can derive accurate  
5 measures of whole body glucose disposal as well as  
6 hepatic glucose production in the basal state and the  
7 suppression of hepatic glucose production, who  
8 responds to insulin.

9 Indirect calorimetry issues to measure  
10 glucose oxidation. If we know what glucose oxidation  
11 is from the tritiated glucose data we know the total  
12 amount of glucose disposed by all the tissues in the  
13 body.

14 The difference between these two values --  
15 total glucose disposal, glucose oxidation -- gives us  
16 a measure of what we call non-oxidative glucose  
17 disposal, which we've shown by muscle biopsies in NMR  
18 to basically be equivalent to glycogen formation.

19 We also looked at the percent body fat by  
20 underwater weighing in triated water. And using NMR  
21 spectroscopy we looked at the amount of fat within the  
22 abdomen -- visceral fat -- and we also looked at

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1 subcutaneous abdominal fat.

2 We paid a lot of attention to fat deposits  
3 versus total body weight because there is a  
4 significant amount of data that says that the amount  
5 of fat within the abdominal cavity may have a specific  
6 role in the development of insulin resistance.

7 These show you the laboratory measurements  
8 at the start of the study. In the control group the  
9 hemoglobin A1c on mean was 5.5. As you can see, in  
10 the bromocriptine group the hemoglobin A1c is  
11 increased but it's, in the placebo group, similarly  
12 increased by about three percent here.

13 An important thing to note is that the  
14 diabetics had very mild, fasting hyperglycemia, and  
15 hepatic glucose production typically we've shown  
16 previously, does not start to rise until the fasting  
17 glucose gets to be about 140. So we're really at the  
18 sort of borderline here where basal hepatic glucose  
19 production starts to go up.

20 Fasting insulin, very typically diabetics  
21 are hyperinsulinemic and you can see that there's no  
22 difference in the insulin levels between the

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1 bromocriptine and the placebo-treated group, and free  
2 fatty acids were similar in all of the groups.

3 Now, to start off I won't show you these  
4 data. Body weight was constant, the BMI was constant,  
5 the percent body fat was constant. There were no  
6 statistically significant changes in visceral or  
7 subcutaneous abdominal fat, although in the placebo  
8 group there was a tendency for the visceral and  
9 subcutaneous abdominal fat to go up. The P value was  
10 at about .1.

11 Now, this shows you the change in hemoglobin  
12 A1c from baseline in the two groups. In the  
13 bromocriptine group, remember the starting hemoglobin  
14 A1c was basically the same in the two groups. In the  
15 bromocriptine group the hemoglobin A1c declined by 7.6  
16 percent, whereas in the placebo group it increased by  
17 .5.

18 This decline is statistically significant in  
19 and of itself. This increase is statistically  
20 significant in and of itself, and obviously the  
21 difference between the two groups is statistically  
22 significant.

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1                   Now, this shows you the time-related change  
2                   in hemoglobin A1c. There's in the first four weeks,  
3                   a decline in both groups, but then the hemoglobin A1c  
4                   starts to go up in the placebo group and ends up above  
5                   where they start. Whereas in the bromocriptine group  
6                   the hemoglobin A1c declines and it stays down.

7                   This shows you the change in fasting glucose  
8                   concentration from baseline. In the bromocriptine-  
9                   treated group it fell by 12 milligrams/deciliter, the  
10                  fasting glucose; whereas it went up by 40 in the  
11                  placebo-treated group.

12                  This shows you the mean glucose during the  
13                  oral glucose tolerance test. In the bromocriptine-  
14                  treated group it fell by 22 milligrams/deciliter; it  
15                  went up by about 25 milligrams/deciliter in the  
16                  placebo group. And this difference, as well as the  
17                  difference in the fasting, are statistically  
18                  significantly different.

19                  Now, this shows you the time-related change  
20                  in the fasting plasma glucose concentration. You can  
21                  see that in the placebo group there's a tendency for  
22                  it to drop and then it goes up here. And then in the

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1 bromocriptine group it drops and it remains down. So  
2 that the changes in fasting glucose pretty much  
3 parallel the changes in the hemoglobin A1c.

4 Now, there were no significant differences  
5 in either the fasting plasma insulin or C-peptide  
6 concentrations, or the insulin or C-peptide  
7 concentrations during the glucose tolerance test.

8 So basically what we're seeing is an  
9 improvement in the fasting glucose and the glucose  
10 tolerance test without any change in insulin or C-  
11 peptide levels.

12 Now, I'd like to show you the insulin clamp  
13 data. During the first step of the clamp the level of  
14 insulin really has very little stimulatory effect in  
15 the diabetic's total glucose disposal. There were no  
16 changes in the pre- and post-, neither the  
17 bromocriptine nor the placebo group.

18 I'm going to show you the data during the  
19 second step of the insulin clamp. So this is the rate  
20 of insulin-mediated, total body glucose disposal  
21 control subjects for reference as shown here to the  
22 left in the pink.

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1           The bromocriptine-treated group, there was  
2           an increase from about 6.5 up to about 8.4. This is  
3           milligram per kilogram fat-free mass per minute. And  
4           this increase, albeit small, is statistically  
5           significant. In the placebo-treated group there was  
6           a decline in insulin sensitivity between the pre- and  
7           the post-study. And this decline in and of itself was  
8           statistically significantly different.

9           If you compare the increment, the  
10          improvement in insulin sensitivity in the  
11          bromocriptine group versus the decrement in the  
12          placebo, this of course is highly statistically  
13          significant at the .01 level.

14          This shows you the rates of insulin-  
15          mediated, non-oxidated glucose disposal during the  
16          insulin clamp. This primarily represents, as I said,  
17          earlier glycogen formation. The control group again,  
18          in pink for reference. The diabetics obviously, have  
19          a decrease in insulin-mediated glucose, insulin-  
20          mediated glycogen formation.

21          Bromocriptine treatment increases this  
22          significantly and in fact, essentially all of the

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1 improvement in whole body insulin sensitivity is due  
2 to an improvement in this non-oxidated glucose  
3 disposal of glycogen formation.

4 There was no change in glucose oxidation  
5 whatsoever. In the placebo-treated group there is a  
6 significant decline in non-oxidated glucose disposal.  
7 This entirely accounts for all of the decrease in the  
8 whole body insulin-mediated glucose disposal.

9 And the difference in the increment in non-  
10 oxidated glucose disposal of glycogen formation here  
11 in the bromocriptine group versus the decrement here  
12 in the placebo group, is highly, statistically  
13 significant.

14 Now, the next slide shows the data on  
15 hepatic glucose production in the controls, in the  
16 basal state -- the solid bars -- and in the diabetics  
17 in the placebo and in the bromocriptine. And again,  
18 this is expressed per fat-free mass.

19 There are no differences in the basal rate  
20 of hepatic glucose production, and again, it's not so  
21 surprising because the fasted glucose was really not  
22 increased in a major way. And during the three steps

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1 of the clamp there's a normal suppression in hepatic  
2 glucose production. No differences between any of the  
3 groups.

4 So in conclusion, compared to placebo,  
5 bromocriptine treatment improves the fast in glucose.  
6 The mean plasma glucose during the oral glucose  
7 tolerance test, the hemoglobin A1c, and it also  
8 improves the total body rate of insulin-mediated  
9 glucose disposal and all of the improvement in whole  
10 body insulin sensitivity is because of an improvement  
11 in the pathway of non-oxidative glucose disposal,  
12 which primarily represents glycogen formation.

13 That's the last slide. I think we can turn  
14 the projector off and put the lights on.

15 CHAIRMAN SHERWIN: Ralph, you did not  
16 present the 40 milli-unit data. And is it just no  
17 change at all?

18 DR. DeFRONZO: Absolutely no change in all.  
19 These --

20 CHAIRMAN SHERWIN: And the insulin levels  
21 during the clamp --

22 DR. DeFRONZO: It's 82 microunits per ml

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1 during the first step of the clamp and basically  
2 similar in the control in the two diabetic groups.  
3 And about 350 during the second step of the clamp.

4 In Mexican-Americans, in this population  
5 that we normally work with, during step one, or  
6 increasing the insulin by 80 microunits per ml, you  
7 don't see the increase in whole body glucose disposal.

8 So the first step may be a little bit higher  
9 than you're normally used to seeing because we don't  
10 get any increase in glucose disposal. This Hispanic  
11 population is very, very resistant to insulin, so we  
12 use a plus-80 and then a plus-350 where the data that  
13 you may be more accustomed to using is, the first step  
14 is an increase in about 20 to 25 microunits per ml,  
15 and then go into 80 to 100 microunits per ml.

16 CHAIRMAN SHERWIN: Did you look at  
17 suppression of fatty acids?

18 DR. DeFRONZO: We did, and we did not see  
19 any difference in the decrease in FFA level in any of  
20 the -- between any of the groups -- the control, the  
21 bromocriptine-treated group, or the placebo-treated  
22 group. I didn't show those data but there's

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1 absolutely no difference between them.

2 CHAIRMAN SHERWIN: Do you have any -- I  
3 mean, there was a substantial difference in  
4 glycohemoglobin; the Ms are modest.

5 DR. DeFRONZO: Yes.

6 CHAIRMAN SHERWIN: Do you think that there's  
7 any effect on insulin secretions or other counter-  
8 regulatory hormones?

9 DR. DeFRONZO: Obviously, we have the data  
10 on insulin and on C-peptide at every 2- to 4-week  
11 intervals, then we have it during the OGTs. And we  
12 really didn't see any change at all in insulin  
13 secretion or C-peptide.

14 The second part of your question in terms of  
15 other counter-regulatory hormones -- we didn't look at  
16 them so I cannot answer that part of the question for  
17 you.

18 CHAIRMAN SHERWIN: Because you know, one of  
19 the issues that had been at least implied in the pre-  
20 clinical data, relates to sympathetic activity and  
21 effects that might be occurring. And yet so far I  
22 haven't seen any data that look at that. Did you look

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1 at norepinephrine or --

2 DR. DeFRONZO: No, we didn't measure those  
3 levels at all, and I think if we were going to do that  
4 we would have to probably do it in --

5 CHAIRMAN SHERWIN: Redesign.

6 DR. DeFRONZO: Yes, redesign the study in a  
7 different way and probably use triated norepinephrine  
8 turnover. These obviously are very, very important  
9 issues and they're issues that we are planning to do,  
10 but at the present time we don't have that information  
11 for you. But they are key questions.

12 DR. DAVIDSON: Ralph, I have a couple of  
13 questions.

14 CHAIRMAN SHERWIN: Yes, Dr. Davidson.

15 DR. DAVIDSON: Jaime Davidson. From  
16 baseline, the decrease in the Alc was .5/.6 percent.

17 DR. DeFRONZO: Point-6, right. And that was  
18 significant, in and of itself. Right.

19 DR. DAVIDSON: The fasting decreased around  
20 10 to 12 and the mean glucose about 22. You know, and  
21 the best that you saw in the study was at four weeks,  
22 but after four weeks the fasting glucose started to go

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1 up for the duration of the study.

2 I don't know if that is statistically  
3 significant because I couldn't see well the numbers.  
4 And my real question is, you know, are those  
5 differences that can be explained on the basis that,  
6 you know, body mass index and weight in the placebo  
7 group was higher than in the groups --

8 DR. DeFRONZO: The point that you are making  
9 -- obviously what you're getting at is an important  
10 one -- is, are there differences in body weight that  
11 can explain these changes. Now, it's true that there  
12 was a slight difference in the body weight in the two  
13 groups before they started, but the fact is that the  
14 body weight remained constant in each group. And that  
15 really is the key thing.

16 So it's not appropriate to sort of look at  
17 the difference between groups. What you need to see  
18 is, in a different group, was there a change in body  
19 weight that could explain the change in fast and  
20 glucose in hemoglobin A1c?

21 In each group the body weight was maintained  
22 quite constant. Now, the only trend was that there

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1 was a trend for an increase in visceral fat mass in  
2 the placebo-treated group. And that was the only  
3 trend in the data at all.

4 So with regards to that, one might argue  
5 that perhaps part of the decrease in insulin  
6 sensitivity that you're seeing in the placebo was  
7 related to that. But the total body weight in that  
8 group was rock-stable. They didn't change at all.

9 In fact, we were a little bit surprised to  
10 see with the constancy of body weight -- in the  
11 placebo group, anyway -- this tendency for visceral  
12 fat to do up a little bit.

13 DR. DAVIDSON: Have you prolonged the  
14 studies past the 16 weeks? Do you have any more data  
15 to see what happened to the glucose levels after 16  
16 weeks?

17 DR. DeFRONZO: No. In fact, we just  
18 completed the studies within the last couple of weeks  
19 so we don't have any data on that. You will see some  
20 longer-term follow-up data from the larger clinical  
21 studies. Remember, this is a relatively small,  
22 mechanistic study.

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1 CHAIRMAN SHERWIN: Dr. Marcus.

2 DR. MARCUS: As someone who doesn't play in  
3 the clamp waters, I'm just curious about the idea that  
4 essentially the effect you saw was attributable to  
5 non-oxidated glucose disposal which you say is  
6 glycogen synthesis. Presumably that represents both  
7 liver and muscle glycogen synthesis.

8 How is that something that could be --  
9 increased glycogen production be a stable result that  
10 goes for 24 weeks? If you were to do muscle or liver  
11 biopsies would you see those organs packed full of  
12 glycogen? Or is there an increase in flux in and out  
13 of that pool?

14 DR. DeFRONZO: Remember, this is a study at  
15 a given point in time. It would be sort of like  
16 eating. When you eat your insulin goes up. Where  
17 does that glucose go? Well, during the clamp about  
18 one-third of the glucose goes into the oxidative  
19 pathway and two-thirds goes into the glycogen  
20 synthetic pathway --

21 DR. MARCUS: That's normally?

22 DR. DeFRONZO: And this is normally. If you

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1 look at diabetes or you look at obesity, what you find  
2 characteristically -- we've described this many, many  
3 years ago and it's a pretty consistent finding -- that  
4 the major defect is always in the glycogen synthetic  
5 pathway.

6 If you look at the offspring, the normal  
7 glucose-tolerant, insulin-resistant offspring of two  
8 diabetic parents, or if you look at first degree  
9 relatives of diabetics, or if you look at people who  
10 are simply obese with normal glucose tolerance, what  
11 you characteristically find is the oxidative pathway  
12 is intact and that the glycogen synthetic pathway is  
13 knocked out.

14 And about -- I guess it's now, about eight  
15 years or so ago, Jerry Shulman and I did a study using  
16 NMR versus the clamp technique where we looked at non-  
17 oxidative glucose disposal as I've described to you,  
18 and using NMR quantitative glycogen formation in  
19 muscle. And we could show that these basically were  
20 identical.

21 So non-oxidative disposal as we measure it  
22 here is really reflecting glycogen formation in

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1 muscle. And this is the characteristic defect you see  
2 in literally all insulin-resistant states.

3 Now, in you or I when we eat we put the  
4 glucose into muscle as glycogen but then two or three  
5 hours later what happens is we break down that  
6 glycogen in muscle and we release that glucose.

7 And if you're missing your plane -- I'm  
8 usually late for everything these days -- and you bolt  
9 through the airport, you contract that muscle, you  
10 break down the glycogen, you use it. So you're not  
11 continuously overloading the muscle with glycogen.  
12 You're storing it during the insulin state, breaking  
13 it down and using it later.

14 CHAIRMAN SHERWIN: Maria.

15 DR. NEW: This is Maria New. Did you  
16 measure cortisol at any time during insulin clamp?

17 DR. DeFRONZO: No. We didn't. We have many  
18 times in the past, and we have never seen a change  
19 during the two to three hour euglycemic clamp in  
20 cortisol levels.

21 On the other hand with regard to the  
22 question that Dr. Sherwin asked, and this is a very

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1 important one, when you infuse insulin at the levels  
2 that we're using, you don't see much of a change in  
3 plasma epinephrine, but you generally see about a 30  
4 percent increase in norepinephrine levels.

5 And if you do titrated norepinephrine  
6 turnover you can see literally two- to three-fold  
7 increases in norepinephrine at turnover. So I think  
8 this is an issue that clearly needs to be explored,  
9 but it needs to be explored I think, using radio-  
10 labeled catecholamines to look at the norepi turnover.

11 DR. NEW: Am I correct in saying that if  
12 this bromocriptine was working at the D<sub>2</sub> receptor  
13 you'd expect a fall in cortisol which might account  
14 for the disposal of the glucose to glycogen that  
15 you've described?

16 DR. DeFRONZO: Yes. Oh, on a chronic basis  
17 that might be true, but in response to insulin  
18 acutely, we would not expect a change in the cortisol  
19 levels. And Anthony will address the issue of -- they  
20 have generated, using diurnal variations, a large  
21 amount of data looking at various hormones as part of  
22 this study, and I'm sure he will share that data with

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1 you. But we didn't measure it acutely during the  
2 clamps.

3 CHAIRMAN SHERWIN: Dr. Critchlow.

4 DR. CRITCHLOW: Are these patients not being  
5 treated? I mean, I noticed in the placebo group the  
6 HbA1c was going up.

7 DR. DeFRONZO: No, this is an actually  
8 rather characteristic finding. If you look at, for  
9 instance the vlibecloamide data, the glucotrol XL data,  
10 and MRL studies, and most recently with troglitazone,  
11 in the placebo group in all of these studies which  
12 have recently been reviewed here, there tends to be a  
13 rise in glucose in hemoglobin A1c in the placebo  
14 group.

15 Actually, if you look at the troglitazone  
16 data the mean rise in hemoglobin A1c and their  
17 monotherapy data rose by about, I believe it was 1.3  
18 and 1.4 percent. So it actually can be rather  
19 significant depending upon how you design the study.

20 So I tried to present the data so that you  
21 could see that there was a drop in hemoglobin A1c from  
22 baseline of .6; the placebo went up in hemoglobin A1c

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1 by .5; and the total difference is 1.1. So that you  
2 could see all of the data and you could make your own  
3 take-home message for it.

4 But there is characteristically an increase  
5 in these parameters in the placebo treatment.

6 CHAIRMAN SHERWIN: Ralph, that reminded me  
7 of a question I forgot to ask you. In your earlier  
8 presentation you mentioned that seven or eight, or  
9 something like that, of the placebo group were on  
10 sulfonylureas, and either 15 were on sulfonylureas in  
11 the bromocriptine group.

12 DR. DeFRONZO: Right.

13 CHAIRMAN SHERWIN: But you didn't tell us,  
14 were they continued or withdrawn from that --

15 DR. DeFRONZO: No, we were very careful.  
16 You asked again -- Dr. Sherwin is a very astute  
17 leader. He knows that if you do these studies and you  
18 withdraw the sulfonylurea, that's a disaster in my  
19 opinion, with all previously designed studies.

20 So we maintain the sulfonylurea throughout.  
21 Now in addition, I've done a subanalysis of the people  
22 who were on sulfonylurea versus the people who are

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1 not. And basically there's no difference.

2 You see a modest increase in insulin  
3 sensitivity literally in every one of the patients,  
4 including the seven who are not on sulfonylureas and  
5 the eight who are on sulfonylureas. So I've already  
6 done that subanalysis and there's no difference. A  
7 very, very key question.

8 CHAIRMAN SHERWIN: Thank you. Mark.

9 DR. MOLITCH: Two questions, Ralph. One,  
10 what was the dose of bromocriptine at that 4-week  
11 point in time where you had maximal effect?

12 DR. DeFRONZO: It would be about 3.2.

13 DR. MOLITCH: And that was then at that  
14 point, kept steady? Or did you continue to increase?

15 DR. DeFRONZO: We increased two more doses  
16 up for the next two weeks. All patients got up to the  
17 maximum dose and there were no significant side  
18 effects. No one was not able to tolerate the --

19 DR. MOLITCH: But your maximal effect looked  
20 like it occurred at 3.2 milligrams at four weeks?

21 DR. DeFRONZO: Well, that's a little bit  
22 difficult to say because remember, the placebo group

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1 tended to get worse. So remember, we went down and we  
2 kind of stayed down. So you could argue that if the  
3 group that's on the bromocriptine were like the  
4 placebo group, they should have gotten worse.

5 So if you were just to follow that out you  
6 would expect that maybe you would have gotten a  
7 continued decline in hemoglobin A1c, and that like the  
8 placebo sort of, there was a time-related factor for  
9 things to get worse.

10 So I wouldn't necessarily extrapolate that  
11 that's the dose at which we got the maximum effect.

12 DR. MOLITCH: And I just wanted to follow up  
13 on Dr. Marcus' question. Perhaps either you or Dr.  
14 Sherwin could really explain clamps to me a little bit  
15 better. I just want to sort of finalize exactly what  
16 the increase in glycogen formation does relative to  
17 the drop in hemoglobin A1c. Does that fully explain  
18 all the effects that cause a decrease in hemoglobin  
19 A1c? How does that happen?

20 DR. DeFRONZO: Well, obviously there are a  
21 number of ways in which you can improve the mean  
22 glucose level during the day. One way would be to

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1 suppress basal hepatic glucose production and the fast  
2 in glucose would drop.

3 We did not see a change in basal hepatic  
4 glucose production, but again the basal hepatic  
5 glucose production was not altered.

6 A second way would be that each time you eat  
7 you take up the glucose more effectively. And when  
8 you take up the glucose more effectively, of course  
9 the mean excursion of glucose is not as high. So the  
10 mean glucose level during the day would not be as  
11 high.

12 So the improvement in glycogen formation  
13 would be a way of improving glucose tolerance --  
14 that's the pathway. And then the net result of the  
15 improved glucose tolerance is that you have a lower  
16 hemoglobin A1c. So what we were trying to do is to  
17 look at a mechanistic way -- we know that in the study  
18 the whole body insulin sensitivity is improved -- we'd  
19 like to know basically is that oxidation or glycogen  
20 synthesis.

21 DR. MOLITCH: So translating that to  
22 clinical use, you expect to see primarily an effect on

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1 post-prandial glucose levels?

2 DR. DeFRONZO: We also saw a decrease in  
3 basal hepatic glucose -- I'm sorry, we saw a decrease  
4 in the fasting glucose as well. So we would expect to  
5 see increases both based on the data that's here, but  
6 the insulin data per se, would be translated to the  
7 post-prandial step.

8 CHAIRMAN SHERWIN: So you know more about  
9 clamps than you thought, Mark. Jules.

10 DR. HIRSCH: Many of the data that you're  
11 showing are exquisitely sensitive to weight changes  
12 and also to changes in carbohydrate intake.

13 And obviously, when you say that placebo  
14 group or the other group, the means -- that must be  
15 the case, but nevertheless there's a distribution  
16 around the means, so I wonder to what degree you look  
17 carefully at correlational or regressional indices of  
18 all of these things going on to see if there's  
19 absolutely no relationship, weight change, in that  
20 sense?

21 DR. DeFRONZO: Yes, which is a very good  
22 question. Now obviously, right from the very

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1 beginning the way we designed the study, we were  
2 critically aware of this issue, and that's why we were  
3 having them meet with the dietician every one to two  
4 weeks to make sure.

5 They would bring in their dietary log, they  
6 would review it with the dietician, she would make  
7 sure in fact, they were being weighed in. So we  
8 basically at least 2-week intervals, sometimes  
9 shorter, had measurements of body weight. There's  
10 absolutely no change, no trend.

11 The mean didn't change because some people  
12 went up and some people went down. They literally all  
13 were within .2 to .3 kilograms of their body weight to  
14 begin with. We measured total body fat by underwater  
15 weighing, which is very sensitive, by triated water.  
16 We also did it by impedance densitometry.

17 And in fact, all three of those measures  
18 consistently showed absolutely no difference in  
19 percent body fat. And with regards to visceral and  
20 subcutaneous fat which we measured using the NMR, the  
21 only tendency at all was for visceral fat mass to  
22 increase a little bit in the placebo group. In the

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1 bromocriptine-treated group it didn't change at all.

2           So I feel very comfortable -- we've  
3 obviously done the regression analysis. There's  
4 nothing that even is remotely hinting that there's any  
5 relationship to changes in either total body weight or  
6 percent body weight or where the fat is in the  
7 abdominal area -- visceral or subcutaneous.

8           CHAIRMAN SHERWIN: Before you leave I just  
9 have one other question that came to mind. You did  
10 glucose tolerance tests on these people --

11           DR. DeFRONZO: Yes.

12           CHAIRMAN SHERWIN: -- and you measured the  
13 circulating insulin. What was the mean level on that  
14 relative to your clamp studies with the different --

15           DR. DeFRONZO: Yes, the mean level during  
16 the OGTT was about 50 microunit per ml in the  
17 periphery. In the first step of the clamp it was 80  
18 and then the second step was about 350.

19           Okay, thank you.

20           CHAIRMAN SHERWIN: Thank you, Ralph. I  
21 appreciate it; that was lovely data, actually. It's  
22 nice to see real scientific data.

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1                   Now, I don't mean to -- no, that's not what  
2 I meant. I mean, it was nice to see new studies that  
3 we have not seen before.

4                   DR. CINCOTTA: Okay, I'd like to carry on  
5 now, moving to the clinical efficacy portion of our  
6 presentation. Before I begin the presentation of our  
7 clinical data I'd just like to point out to you, bear  
8 in mind as we're going through the presentation of  
9 these results the continuity and the response  
10 characteristics to this drug, because it's been  
11 demonstrated across species and within humans across  
12 several different studies including the results of the  
13 studies from the clamp that Dr. DeFronzo just shared  
14 with all of us.

15                   The Phase 3 studies representing our pivotal  
16 data were comprised of three different trials --  
17 studies K, L, and M. And the clinical development  
18 focus depicted on the slide was obviously in the  
19 treatment of Type 2 diabetes to reduce hyperglycemia.

20                   And it was assessed by one, improvement in  
21 glycemic control via HbA1c reductions from the  
22 baseline relative to an appropriate control group, and

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1 secondly, in changes in fasting and post-prandial  
2 glucose levels relative to the control group.

3 Additionally, because of the results we are  
4 finding in our animal model systems, we looked for  
5 possible additional benefits in this diabetic  
6 population in terms of reducing both fasting and post-  
7 prandial free fatty acid levels, as well as the  
8 fasting and post-prandial triglycerides.

9 Again, the adjunctive therapy studies were  
10 studies K and L where we were adding Ergocet™ to  
11 sulfonyl -- stable doses of sulfonylurea. In study M  
12 we were investigating the effects of Ergocet™ on  
13 hyperglycemia in individuals where it was the only  
14 anti-diabetic agent on board.

15 The studies were essentially designed to  
16 test the hypothesis, but a population of diabetics  
17 treated with Ergocet™ would display an improvement in  
18 metabolism relative to a similar population exposed to  
19 the same experimental conditions.

20 The next slide then, demonstrates key  
21 features of the study design for adjunctive therapy  
22 studies. Individuals in these trials were on weight-

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1 maintaining diets at randomization, maintained on  
2 those diets throughout the 24-week treatment period.

3 And this was done primarily by means of  
4 dietary monitoring and intervention to maintain their  
5 caloric consumption at the isocaloric weight  
6 maintaining level. In fact, it was successful in that  
7 there were no clinically relevant changes in body  
8 weight on average, for the Ergocet™ or placebo  
9 groups, start to finish, in either of the adjunctive  
10 therapy studies or in the monotherapy study.

11 Additionally, stable doses of sulfonylurea  
12 were maintained for a minimum of 60 days prior to  
13 study entry and then beyond the entry into the study,  
14 throughout the course of the study, dose and the type  
15 of sulfonylurea was maintained.

16 The next slide demonstrates the design of  
17 our Phase 3 studies in terms of dosing regimen. There  
18 was a 2-week screening period. At week zero,  
19 randomization, individuals were force titrated over a  
20 6-week period at .8 milligrams per week, up to the  
21 final dose of 4.8 milligram per day, and continued on  
22 that maintenance dose to the end of the study.

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1           If individuals were unable to be titrated up  
2 to the maximum dose of 4.8 milligrams for whatever  
3 reason, they were allowed to remain in the study as  
4 long as the minimum dosage was 1.6 milligram per day.

5           The next slide demonstrates the key  
6 inclusion criteria in these studies: Type 2  
7 diabetics; HbA1c 7.8 to 12.5; BMIs to overweight,  
8 obese individuals; they had to have a stable body  
9 weight for a minimum of 30 days prior to study entry;  
10 between the ages of 30 and 72; and euthyroid.

11           The key exclusion criteria for the  
12 adjunctive therapy studies, included women that were  
13 pregnant, lactating or less than one year post-partum,  
14 or individuals on the following medications: insulin,  
15 sympathomimetics because they interact with our  
16 mechanism of action and actually block the effect of  
17 our drug, daily corticosteroids, beta blockers and  
18 diuretics, or hypolipidemic agents that were altered  
19 within 30 days prior to randomization.

20           We wanted to have everyone on a stable dose  
21 of hypolipidemic agents if they were on any dose at  
22 all, so that we could more accurately assess the

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1 effect of our agent on lipid levels over the course of  
2 treatment.

3 Significant medical illnesses including  
4 renal and liver disease as well as cancer, were  
5 omitted from the trial.

6 The next slide shows the efficacy parameters  
7 used to assess response to Ergocet™ in the Type 2  
8 diabetic population. The primary efficacy variable  
9 was a change from baseline relative to the placebo  
10 control group in HbA1c.

11 Secondary parameters were changed in diurnal  
12 profiles in glucose insulin, free fatty acids in study  
13 L alone where it was measured, and triglycerides --  
14 both in the fasting and the post-prandial states.

15 Study entry at week-zero and then again at  
16 week 24, individuals entered CRO -- Clinical Research  
17 Organization -- where they were subjected to sampling  
18 at one hour before and two hours after standardized  
19 meals on an individual basis, for breakfast, lunch,  
20 and dinner.

21 So we were able to get a pre-meal and two  
22 post-meal samples at all the three meals over the day.

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1       Additionally, fasting total HDL and LDL cholesterol  
2       levels were measured and in one study, body density  
3       was measured via the method of underwater weighing  
4       that Dr. DeFronzo described to you earlier.

5               The next slide shows in fact, in study K,  
6       245 subjects were equally randomized. Of individuals  
7       that were randomized the majority of them were  
8       evaluatable in the intent-to-treat population.

9               In other words they had data of at least  
10       four weeks into the study that could be carried  
11       forward if they did drop out prior to termination at  
12       week-24. However, roughly 76 and 86 percent Ergocet™  
13       and placebo subjects finished this trial.

14               Study L -- this was a very similar design,  
15       very similar results, fairly balanced study; 74 and 86  
16       percent of all individuals completing the trial.

17               The baseline characteristics on this slide  
18       demonstrate that sex distribution is approximately the  
19       same between Ergocet™ and placebo in each study --  
20       study K and study L -- roughly 75 percent male, 25  
21       percent female.

22               The majority of the subjects were white.

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1           However, we do have -- these are percentages now, not  
2           n numbers -- percentages of Black and Hispanics  
3           distributed equally among the two groups in both  
4           studies. The average age was roughly 55 years.

5                     The next slide shows BMIs, as most of our  
6           studies are obese, on average, Type 2 diabetics. BMI  
7           of roughly 32. And the sulfonylurea usage was  
8           approximately 90 percent -- across all four arms were  
9           glyburide or glypizide.

10                    The duration of the disease is roughly five  
11           to six years, on average, and no change, no  
12           difference, between either arm in either study.

13                    Finally, metabolic characteristics in  
14           studies K and L are demonstrated on this slide.  
15           Individuals incoming, HbA1c values were approximately  
16           9.4 across the studies. And poor control and the  
17           blood glucose levels obviously, to reflect that --  
18           approximately 220 milligrams per deciliter.

19                    However, they were hyperinsulinemic; plasma  
20           insulin levels around 25 microunits per ml. The  
21           fasting triglyceride levels were also elevated --  
22           approximately 250 milligrams per deciliter. And in

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1 one study where it was measured, the fasting and free  
2 fatty acid levels are around 800 micromolar -- also  
3 elevated compared to the normal population -- where  
4 the upper limit of normal can vary between 500 to as  
5 much as 600 micromolar.

6 The next slide then demonstrates that over  
7 the course of both studies -- in blue, study K and in  
8 red, study L -- subjects, the majority of the subjects  
9 were titrated up to the maximum dosage of 4.8  
10 milligrams. Both studies are roughly 70 to 75 percent  
11 -- the individuals were able to be titrated up to the  
12 4.8 milligram dosage.

13 Having defined the patient population, let's  
14 now look at the result of the studies. And this slide  
15 depicts the change from the placebo control group in  
16 study K, and in study L using a last observation  
17 carried forward analysis, one can see the difference  
18 between the Ergocet™ and the placebo group in the  
19 right-hand column -- 0.5 A1c delta. The P value  
20 underneath it is highly statistically significant.

21 Study L shows a very similar pattern as  
22 study K -- so the data essentially are reproducible.

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1 The 0.6 delta relative to the control group. The P  
2 value again, highly statistically significant, and  
3 obviously the average of the two studies being the  
4 mean.

5 If we look at the data from these studies as  
6 representing the individuals that have completed the  
7 study, the next slide shows that for the individuals  
8 completing the 24 weeks of treatment the numbers are  
9 essentially the same. Study K, 0.5, highly  
10 statistically significant, delta decreased relative to  
11 the placebo group. For study L a 0.63 decrease  
12 relative to the placebo group -- again, highly  
13 statistically significant. And again, the average of  
14 the two studies combined.

15 So in two independent studies basically  
16 demonstrating a similar response in change, in HbA1c,  
17 or an improvement in HbA1c relative to our control  
18 group. If we look at the data over time, in study K  
19 we see that the study effect begins to occur early on  
20 at four to eight weeks; it reaches its maximum effect  
21 in study K at 12 weeks; maintained throughout.

22 And in study L we see a very similar

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1 pattern. Study drug effects begins to occur early on.  
2 It's actually statistically significant at week-8 of  
3 the drug treatment. It's maximally effective after 12  
4 weeks of the drug treatment where the delta is  
5 approximately 0.6 relative to the placebo group.

6 And you see that the change relative for the  
7 placebo group or control for this study, is maintained  
8 beyond week-12, Out at week-16, -20, and -24 the  
9 delta is the same. That is, no loss in the  
10 improvement in glycemc control relative to our  
11 control group over that time period.

12 Assuming that the DCCT data assessing  
13 improvement in glycemc control in the Type 1 diabetic  
14 population, can be extrapolated to the Type 2 diabetic  
15 and that the improvement in glycemc control observed  
16 in the 6-month study is maintained relative to the  
17 control, or a long period of time.

18 It can be calculated that the improvement in  
19 glycemc control seen here correlates with a reduction  
20 in microvascular risk -- a reduction in risk of  
21 microvascular disease -- calculated on an individual  
22 basis as a change from baseline; the placebo from

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1 baseline and the Ergocet™ group from the baseline --  
2 of approximately 37 percent.

3 In other words, the reduction in risk being  
4 in the Ergocet™ group versus our control group in  
5 long-term complications in microvascular disease, is  
6 roughly 37 percent, given the initiating A1c values of  
7 approximately 9.4 for these subjects.

8 The next slide demonstrates the changes from  
9 most diurnal samples that I described to you, measured  
10 before and one and two hours after each meal of the  
11 day from early morning at 7 a.m. till late evening at  
12 7 p.m.

13 What we're going to show here for the sake  
14 of time is the results from study K and L pooled  
15 together. However, be aware that the data -- just as  
16 the HbA1c data over time -- are consistent between  
17 study K and L, and they're statistically significant  
18 for each study alone when assessed over the entire  
19 treatment day.

20 Having said that, let's look at the results.  
21 The fasting levels relative to our control group, are  
22 bound by approximately 25 milligram per deciliter, and

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1 the post-prandial levels after breakfast, after lunch,  
2 and after dinner, are also reduced by approximately 25  
3 to 35 milligrams per deciliter.

4 And the fact is significant, as I said, over  
5 the entire portion of the day. So the drug in fact,  
6 given once in the morning, very short half-life,  
7 influences the fasting glucose level and the post-  
8 prandial glucose level. Again, entirely consistent  
9 with the clamp data just presented to all of us by Dr.  
10 DeFronzo.

11 Also consistent with those data are the  
12 results relating to the insulin values over the course  
13 of the day. If one looks at the insulin values for  
14 the placebo and Ergocet™ group, although there is a  
15 slight increase late in the day of approximately four  
16 or five microunits per ml, on average over the entire  
17 day the changes in insulin are not clinically relevant  
18 and are not of any large magnitude, especially when  
19 you're considering the post-prandial values.

20 We now turn to the free fatty acid changes  
21 in these subjects. As in the animal model system  
22 where elevated free fatty acids are present and we

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1 introduced bromocriptine to that situation, we see a  
2 reduction in lipolysis, we see a reduction in the free  
3 fatty acid levels in those model systems.

4 So too, does one see a reduction in free  
5 fatty acid levels of these Type 2 diabetics that did  
6 have those high, elevated levels of free fatty acids  
7 coming into the study. Approximately 800 micromolar,  
8 if you recall.

9 Here in the fasting state reduction of  
10 approximately 150 micromolar relative to the control  
11 group, and then reduction of 150 micromolar is  
12 maintained post-prandially after the breakfast, lunch,  
13 and the dinner meals. Again, statistically  
14 significant across the entire day at the .02 level so  
15 the magnitude of the effect, 150 micromolar, we're  
16 getting down close to the upper end of normal for the  
17 free fatty acid level in humans, and effective across  
18 the entire day.

19 If we now switch to the triglyceride story,  
20 one would suspect that the triglycerides would be  
21 reduced if the free fatty acids are, and as much they  
22 represent a key substrate for triglyceride synthesis

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1 in the liver and re-esterification of free fatty  
2 acids.

3 And in fact, we do see this, and it's in  
4 studies K and L combined here. Don't forget that it  
5 is statistically significant for either study K or  
6 study L alone, independent for each other. The data  
7 here are also reproducible.

8 In fasting, the values have dropped by  
9 almost 80 milligrams per deciliter and across the day,  
10 post-prandially at breakfast, post-prandially after  
11 lunch, and dinner, on average, the delta is  
12 approximately 70 milligrams per deciliter drop.

13 A closer inspection of the triglyceride  
14 effect of this drug in this patient population, we did  
15 an analysis of the triglyceride effect of the drug as  
16 a function of the incoming triglyceride level itself.  
17 And we found that the higher the triglyceride levels  
18 were upon study entry, the larger the response.

19 And actually, we did it with Russian  
20 analysis that was statistically significant and the R  
21 value was approximately 0.6. And you can see that for  
22 individuals, baseline triglyceride values are between

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1 300 and 750 milligrams per deciliter, instead of a 75  
2 mg per deciliter of delta overall.

3 Now for this subgroup you see that there's  
4 a 200 milligram per deciliter reduction in the  
5 triglycerides. Fasting triglyceride levels again, P  
6 value .001. And if we extend this out to those  
7 individuals whose triglycerides were greater than 750  
8 milligrams per deciliter, again, the reduction from  
9 baseline is even larger -- 400 milligrams per  
10 deciliter.

11 And relative to your placebo group, the 300  
12 milligram per deciliter delta, again statistically  
13 significant even though we did not have a lot of  
14 patients to sample from out at these increased levels  
15 of triglycerides.

16 The next slide then, reviews for you in  
17 brief, the importance of reducing hypertriglyceridemia  
18 in the diabetic population. Just a couple of key  
19 facts and this will be expounded on later after my  
20 discussion, by Dr. George Steiner who is with us today  
21 and is an expert in the field of hyperlipidemia in the  
22 general and diabetic populations.

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1           Number one, cardiovascular disease -- I'm  
2           sure you're all well aware -- is the most prevalent  
3           cause of mortality in the diabetic population. And  
4           hypertriglyceridemia is the most common dyslipidemia  
5           in this patient population.

6           Hypertriglyceridemia has been demonstrated  
7           to be an independent risk factor for cardiovascular  
8           disease. The post-prandial lipemia is correlated with  
9           increased severity of coronary artery disease. As  
10          post-prandial levels of triglycerides go up, so too is  
11          the severity of coronary artery disease.

12          Finally, hypertriglyceridemia is associated  
13          with increases in small dense LDL, PAI-1, and  
14          decreases in HDL cholesterol -- all factors that are  
15          themselves, associated with risk for cardiovascular  
16          disease.

17          Finally, the next slide correlates the  
18          triglyceride effect with the changes in the total  
19          cholesterol values in these subjects. We can see  
20          clearly here -- placebo in blue, Ergocet™ in yellow  
21          -- looking at the total there's approximately a nine  
22          milligram per deciliter change in the total

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1 cholesterol level.

2           However, none of this can be attributed to  
3 any change, either in HDL or HDL cholesterol, which  
4 suggests that this delta is due to a change in the  
5 relative amounts of the LDL cholesterol, and is  
6 entirely consistent with a reduction in the total  
7 triglyceride levels. Dr. Steiner will amplify on that  
8 point in his upcoming discussion.

9           Finally, in study K we measured body  
10 density. And in our study where we had 75 subjects on  
11 Ergocet™ to compare to 82 on placebo, we did see that  
12 the body density increased by 001344 kg per liter in  
13 the Ergocet™ group relative to the baseline. It was  
14 statistically significant.

15           The placebo group increased not  
16 significantly significant so there's no change in the  
17 placebo relative to the baseline. The between-group  
18 difference, it shows a positive increase in body  
19 density of almost 001 kg per liter but it did not  
20 reach statistical significance.

21           The bottom line is that Ergocet™ subjects  
22 over a course of time relative to baseline, increased

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1 in body density, which means they're increasing the  
2 lean to fat mass ratio.

3 The next slide then, is a summary of our  
4 data obtained in our adjunctive therapy studies. We  
5 see a significant and clinically relevant reduction in  
6 HbA1c relative to the appropriate control group, from  
7 0.5 to 0.6.

8 There are significant and clinically  
9 relevant reductions in both the fasting and the post-  
10 prandial measured at three meals during the day, of  
11 glucose, free fatty acids, and triglycerides -- all  
12 three. And there were no clinically relevant changes  
13 in the insulin; again, entirely consistent with the  
14 data presented by Dr. DeFronzo during his clamp  
15 studies.

16 I'd like to now move to our monotherapy  
17 study. It has a very similar design as the adjunctive  
18 therapy. Type 2 diabetics however, they are not on  
19 any prior drug therapy with the exception of handful  
20 of subjects who are on sulfonylurea a year-and-a-half  
21 before study initiation.

22 All subjects have not been treated

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1 previously for the disease. HbA1c levels in the study  
2 were slightly lower upon entry; no OHAs and no body  
3 assessment -- no assessment of body composition.

4 The disposition of these subjects again as  
5 in the previous two studies, randomized and well-  
6 balanced. The majority of the patients obtaining  
7 evaluable data, at least in week-4 out into the study.  
8 And again, exactly the same as in the two prior  
9 studies; 75 percent of all subjects completing  
10 relatively the same in the placebo and in the treated  
11 groups.

12 Baseline characteristics of this population  
13 are similar to the adjunctive therapy subjects but by  
14 distribution of sex, again, roughly 75 percent male,  
15 25 percent female; the majority of them white. Again,  
16 however, from the percentage basis we do have a  
17 representation of Blacks and Hispanics. Again, the  
18 mean average age, roughly 55 years.

19 Characteristics of these individuals on a  
20 weight basis: BMI similar to the adjunctive study --  
21 32. Again, on average, obese. Duration of the  
22 disease: somewhat less on average than in the

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1 adjunctive therapy; approximately four years on  
2 average.

3 Baseline characteristics relating to the  
4 metabolic parameters of these subjects: still at core  
5 metabolic control but they're not as bad off as in the  
6 prior adjunctive therapy studies and the blood sugar  
7 levels, although still very elevated are not quite as  
8 high as in the prior study.

9 Insulin levels approximately 22, 23  
10 microunits per ml. The hypoinsulinemic diabetics  
11 without treatment in poor control, and their lipid  
12 levels are not as elevated as in the adjunctive  
13 therapy studies but still high, and very high levels  
14 again, of free fatty acids.

15 Again, as in the adjunctive therapy studies,  
16 both for study K and L, here again we see the same  
17 distribution of subjects titrated to final dosage: 75  
18 percent roughly attaining maximum titration to the 4.8  
19 milligram dose.

20 Let's now turn to the HbA1c change from  
21 baseline for the study relative to the placebo control  
22 group over the 24-week treatment period. Last

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1 observation carried forward analysis, and completer  
2 analysis identifying those subjects that completed the  
3 24-week therapy.

4 You can see .44 decrease relative to the  
5 control group; .02 statistically significant for the  
6 individuals; the subset, the majority actually, that  
7 finished the trial, 24 weeks on therapy, the delta is  
8 .56 relative to your control group. Again,  
9 statistically significant and nearly the same number  
10 for studies for K and L.

11 Again, if we look over time we see a similar  
12 pattern. The changes relative to the placebo group  
13 occur early on, between roughly 8 to 12 weeks, and are  
14 maintained beyond the 12-week period -- the delta is  
15 maintained throughout the course of the study.  
16 There's no loss of the magnitude of the effect  
17 relative to the control over the ensuing 12 weeks.

18 The next slide demonstrates, as in our  
19 adjunctive therapy studies, the fasting glucose levels  
20 and the post-prandial glucose levels are decreased by  
21 approximately 30 to 40 milligrams per deciliter.

22 And it is true, not only after the breakfast

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1 meal but also after lunch, and then after dinner as  
2 well. P value over the entire day, .0012. Entirely  
3 consistent with all previously shown results.

4 Again, diurnal insulin levels as in the  
5 clamp data that were presented by Dr. DeFronzo and the  
6 adjunctive therapy studies that were presented just  
7 earlier, again here, no significant change in the  
8 insulin values relative to the placebo group, across  
9 the entire day.

10 Improvement in glycemic control without  
11 change in the insulin values. The free fatty acid  
12 levels shown on the next slide represents a similar  
13 shift from the control group at the fasting and the  
14 post-prandial values over the entire day.

15 The P value here did not reach statistical  
16 significance, although the magnitude, the direction  
17 and the shape of the curves are essentially the same  
18 as for the adjunctive therapy study.

19 P value is .1 and may be due to the smaller  
20 sample size -- in this study is roughly half of what  
21 we used in the adjunctive therapy.

22 The triglyceride levels similarly were

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1 reduced, but again, did not reach statistical  
2 significance over the day -- .2 relative to our  
3 control group -- although you can clearly see that the  
4 direction and the trends are really similar to what we  
5 saw in our adjunctive therapy studies.

6 Remember that as the incoming triglyceride  
7 dosage increased, so too did the response to the drug,  
8 and these individuals also had lower triglyceride  
9 levels upon study entry relative to the prior  
10 adjunctive therapy studies.

11 The next slide then, summarizes the basic  
12 responses to Ergocet™ in this monotherapy population  
13 that were significant. Reduction in the HbA1c, .56  
14 relative to placebo for individuals completing the 24-  
15 week treatment period; associated with reductions,  
16 approximately 30 to 40 milligrams per deciliter; not  
17 only fasting in the morning but post-prandially after  
18 all three meals -- breakfast, lunch, and dinner.  
19 Again, no clinically relevant changes in insulin.

20 I'd like to now switch gears and discuss a  
21 different but related topic to the efficacy  
22 presentation that we just made, and this relates to an

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1 observation that we made empirically during our Phase  
2 2 studies.

3 And that is that we found, during the course  
4 of treatment in our Phase 2 studies, those subjects  
5 that responded best to Ergocet™ did so very early-on  
6 during the course of treatment.

7 We asked ourselves, if in fact one could  
8 find these individuals early on -- accurately,  
9 reliably, reproducibly, is there a logical reason not  
10 to do so -- we concluded that it could be a clinical  
11 benefit or a clinical tool to the physician to  
12 identify subjects who are going to respond to the drug  
13 long-term if we had a way of finding them early on and  
14 characterizing them.

15 To test the strength of this observation in  
16 our Phase 2 studies, we incorporated a definition for  
17 an early response group prospectively into our Phase  
18 3 program.

19 The next slide here, demonstrates -- again,  
20 the purpose and the intent here was to utilize this  
21 phenomenon of early response to Ergocet™ as a  
22 clinical tool to help the physician identify subjects

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1 most likely to benefit from continued treatment.

2 Prior to breaking the blind in our Phase 3  
3 studies subjects were stratified at week-8 by HbA1c  
4 change from baseline. The early response subgroup was  
5 defined as those subjects whose HbA1c decreased by 0.3  
6 or greater, relative to the baseline.

7 The next slide demonstrates essentially,  
8 what we observed. Now, this is just literally, a  
9 characterization of subjects that met this criteria.  
10 Again, we saw this reproducibly in Phase 2; we wanted  
11 to take advantage of it and possibly utilize it as a  
12 clinical tool if it were appropriate, and so we  
13 employed it into our Phase 3 design.

14 And this data here is merely a description  
15 or a characterization of what happened to those  
16 subjects that met that definition over the 24-week  
17 treatment period.

18 And you can see that in monotherapy and  
19 adjunctive therapy -- here it's K and L combined but  
20 for K and L separately it's the same -- you can see  
21 that over time there is a decrease relative to the  
22 baseline for these subjects, of a 0.65 HbA1c -- both

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1 for the monotherapy study and for the adjunctive  
2 therapy studies.

3 So it has turned out to be, as in our Phase  
4 2 studies, reproducible cross studies in our Phase 3  
5 program. Second important point to realize is that  
6 the .65 drop from the baseline represented an average  
7 of 65 percent of the total Ergocet™ population.

8 In both the monotherapy and the adjunctive  
9 therapy studies this has changed from the baseline --  
10 wanted to make an intra-subject comparison -- was  
11 statistically significant but that's not what the  
12 intent is here.

13 It was just to define and characterize an  
14 early response subgroup to see what, in fact, they  
15 would look like out after 24 weeks of treatment, and  
16 to see if you could reproducibly identify their  
17 response. And you can see here it's very, very  
18 similar for both adjunctive therapy and monotherapy.

19 You may be asking yourselves, what are these  
20 two dots doing here on this graph? The purple dot  
21 right here represents for comparison or reference,  
22 just the placebo -- the all-placebo group -- after the

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1 24-week treatment period.

2 The blue dot represents what we feel is an  
3 appropriate placebo comparison that would be -- that  
4 does consist of an equal distribution of placebo  
5 responder and non-responders as is in this Ergocet™  
6 group.

7 This approach we discussed with the FDA and  
8 its details of its derivation can be provided if  
9 desired, in the Q&A session later on, but the main  
10 point is that this Ergocet™ group consists of placebo  
11 responders and non-responders, and this dot represents  
12 the average weight of a placebo responder/non-  
13 responder group so that you can make a comparison  
14 here.

15 Roughly, the story is the same. The change  
16 relative to the baseline is .65. It's a little  
17 greater -- .8 -- if you compare it to the placebo.  
18 The next slide then, is essentially a summary of HbA1c  
19 reduction from baseline for this early response  
20 subgroup that we characterized.

21 By our definition, it's roughly .65 for  
22 monotherapy and adjunctive therapy -- change from the

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1 baseline. It's a little larger for a reduction from  
2 a comparable placebo group -- approximately on  
3 average, .8.

4 It represents 65 percent of the entire  
5 Ergocet™ group, both in the monotherapy and  
6 adjunctive therapy studies, and its value and intent  
7 was merely to be used as a clinical tool to help the  
8 physician assess those individuals most likely to  
9 derive the long-term benefit from the drug.

10 Therefore in summary, the overall  
11 effectiveness of Ergocet™ is that it does improve  
12 glycemic control both in adjunctive and monotherapy.  
13 And that has been demonstrated by an improvement in  
14 HbA1c and fasting and post-prandial glucoses across  
15 three meals, relative to the placebo control group.

16 It also provides additional benefits in  
17 reducing fasting and post-prandial, free fatty acids  
18 and triglycerides. We were able to define an early  
19 response category that identified a group that would  
20 derive the most metabolic benefit on average, from the  
21 treatment, and from our mechanistic studies in animal  
22 model systems -- the unique CNS mechanism of action

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1 may allow it to be complementary to other modes of  
2 action that work in the periphery.

3 I'd like to leave, finally, with a quote  
4 from Elliott Joslin some 70 years ago saying: "I  
5 believe the chief cause of premature development of  
6 arteriosclerosis and diabetes, save for the advancing  
7 age, there's an excess of fat -- an excess of fat in  
8 the body, an excess of fat in the diet, and an excess  
9 of fat in the blood. With an excess of fat diabetes  
10 begins; from an excess of fat, diabetics die --  
11 formerly of coma, recently of arteriosclerosis".

12 And I would now like to turn it over to Dr.  
13 Steiner who's going to expound on the relevance and  
14 the validity of the quote from Dr. Joslin some 70  
15 years ago, with more recent, actual data.

16 CHAIRMAN SHERWIN: Dr. Cincotta, just want  
17 to be sure I am -- after we get through with the  
18 lipid data we have -- because I don't have quite a  
19 schedule -- then the adverse -- and I don't know how  
20 many speakers are in front of that --

21 DR. CINCOTTA: Yes, the next is safety, and  
22 that ends it.

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1 CHAIRMAN SHERWIN: And that ends it. And  
2 Dr. Steiner, your presentation --

3 DR. CINCOTTA: Is right now; five minutes.

4 CHAIRMAN SHERWIN: That would be my guess.  
5 So maybe we'll have your presentation, then we'll take  
6 a break at that point.

7 Okay, Mr. Molitch has a question, but make  
8 it brief, Mark, because --

9 DR. MOLITCH: Just a couple of questions  
10 about these studies. Are there weight data you have  
11 for the curves that you showed for the entire group,  
12 and then breaking down with the responders and non-  
13 responders?

14 DR. CINCOTTA: Yes, we do. And as I --

15 DR. MOLITCH: Can we see the data?

16 DR. CINCOTTA: The weight data over time for  
17 the entire group?

18 DR. MOLITCH: And then responders versus  
19 non-responders, and also the prolactin data for the  
20 entire group, and also responders versus non-  
21 responders.

22 DR. CINCOTTA: There is the weight data from

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1 studies K, L, and M. Do you have study -- Jeremy --  
2 study K? No. There we do. So this is the weight  
3 change. You can see there's a two pound change in the  
4 body weight for the Ergocet™ relative to the  
5 baseline, and a little less than two pounds relative  
6 to the placebo over time.

7 Don't forget, this was associated with an  
8 increase in the body density, so it's hard to  
9 attribute this light. They weighed 210 pounds so this  
10 represents a one percent increase in body weight. But  
11 the increase in the body density strongly argues that  
12 it's not an increase in body fat.

13 DR. MOLITCH: Do you have that for  
14 responders versus non-responders? In your responder  
15 analysis?

16 DR. CINCOTTA: We don't have that available  
17 right now, no.

18 DR. MOLITCH: And the prolactin data for the  
19 same --

20 DR. CINCOTTA: No, do not.

21 DR. MOLITCH: Are there prolactin data?

22 DR. CINCOTTA: We have the HbA1c effects

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1 relative to incoming prolactins -- whether they were  
2 low or high.

3 DR. MOLITCH: And how about change in  
4 prolactin with your female --

5 DR. CINCOTTA: We don't have the data here,  
6 but there was no correlation between the reduction in  
7 the prolactin and the effect on glycemc control.  
8 Remember, at the 4.8 milligram dose we're reducing  
9 that slight elevation of prolactin down to normal in  
10 nearly every subject.

11 DR. MOLITCH: And how about prolactin -- the  
12 responder versus non responder?

13 DR. CINCOTTA: No difference.

14 DR. HIRSCH: Just a question about the  
15 density data while we're on that. That was only done  
16 with the Ergocet™? The density measures -- right  
17 here -- Jules Hirsch. The density measures were only  
18 done on the treatment group and not on the placebo?

19 DR. CINCOTTA: No, we did it on the placebo  
20 group as well. There was no change from --

21 DR. HIRSCH: There was no density -- how do  
22 you interpret the density change in the absence of a

1 weight change? What do you think that --

2 DR. CINCOTTA: For the placebo group there  
3 was no change in body weight, no change in density.  
4 For the Ergocet™ group there was a slight, 2-pound  
5 increase as you can see from the slide here, in body  
6 weight, and a slight increase in body density.

7 DR. HIRSCH: Which you interpret as -- I  
8 mean, a change in density in the absence of --

9 DR. CINCOTTA: Lean to fat --

10 DR. HIRSCH: I beg your pardon?

11 DR. CINCOTTA: An increase in the lean to  
12 fat mass ratio.

13 DR. HIRSCH: So you figure it's a loss of  
14 fat so there's more muscle mass, therefore?

15 DR. CINCOTTA: Right. By the way, just as  
16 a point of note, in the animal model systems, we and  
17 several other laboratories clearly demonstrated that  
18 bromocriptine treatment does increase the lean to fat  
19 mass ratio over time, and that the treatment with the  
20 drug is proteogenic. It's a proteogenic.

21 CHAIRMAN SHERWIN: Oh, I'm sorry, Dr.  
22 Davidson.

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1 DR. DAVIDSON: One question. You know, if  
2 we look at your data from baseline at 24 weeks,  
3 there's really very little decrease in A1c. However,  
4 in your responder data you say 65 percent of all your  
5 patients were really -- those good responders.

6 Does that mean that 35 percent of these  
7 patients actually did worse in order to get that data?

8 DR. CINCOTTA: No. Actually, the responder  
9 group does represent 65 percent of all the subjects.  
10 The non-responder portion, the 35 percent, on average  
11 was -- on average -- was similar to the placebo group  
12 at the end of the 24-week treatment period.

13 DR. DAVIDSON: Thank you.

14 CHAIRMAN SHERWIN: Dr. Steiner.

15 DR. STEINER: Well, thank you very much for  
16 asking me to join with you. My task today is to  
17 discuss triglycerides and atherosclerosis in very broad  
18 terms, and I'd like to make five points and I'll try  
19 to keep it fairly straightforward to those.

20 First, that hypertriglyceride being and is  
21 a risk for coronary disease; second, that  
22 hypertriglyceridemia is increasingly being found to be

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1 a risk for coronary disease in people with diabetes;  
2 third, that there is a debate as to whether  
3 hypertriglyceridemia is a risk because of the  
4 triglyceride-rich lipoproteins themselves for --  
5 because of the associated factors that are marked by  
6 the presence of hypertriglyceridemia, but that this  
7 really doesn't matter because even those factors are  
8 reversed when one treats hypertriglyceridemia; fourth,  
9 that there is beginning to emerge a body of data that  
10 suggests that reducing plasma and triglycerides is  
11 beneficial in terms of atherosclerotic cardiovascular  
12 disease; and fifth, to suggest to you the hints that  
13 are presently in existence and some of the studies  
14 ongoing with respect to hypertriglyceridemia in  
15 diabetes and the effects if we're using plasma  
16 triglycerides on coronary disease in diabetes.

17 So if we can have the first slide, please.  
18 And I'll just do this in five slides, one for each  
19 point.

20 This is a meta-analysis that Melissa Austin  
21 has conducted looking at men and women attempting to  
22 dissect out whether there is an independent effect of

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1 triglyceride -- independent of HDL or not.

2 She looked at studies which conducted uni-  
3 variate analysis and studies which conducted multi-  
4 variate analysis. There were six studies in men that  
5 she examined the data from, and two in women.

6 And when she did multi-variate analysis on  
7 these she found that independent of HDL, an increase  
8 of one millimole of triglyceride in men increased the  
9 relative risk of coronary disease by about 17 percent,  
10 and in women by about 34 percent.

11 Although we don't have any data to suggest  
12 the reverse, it's tempting to speculate that maybe a  
13 reduction of one millimole might reduce the risk of  
14 coronary disease by this amount as well.

15 If we look at the situation in those with  
16 diabetes the first hint at this came from the World  
17 Health Organization. A more definitive prospective  
18 hint came from the studies in the Paris prospective  
19 study in which men with impaired glucose tolerance or  
20 diabetes were characterized and then subsequently  
21 followed for 11 years. And the differences between  
22 those who died from coronary heart disease compared to

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1 those who did not, was examined.

2 And it was found that independently the  
3 people who died with coronary heart disease were found  
4 independently to have higher triglyceride levels.

5 Unfortunately, this study did not examine  
6 HDL levels but more recently a study conducted by Mark  
7 Olaxo in a Finnish population has looked at the people  
8 with diabetes and found that those who died of  
9 coronary heart disease had both high VLDL and low HDL  
10 levels; which would be consistent with this whole  
11 picture.

12 Now as I said, we don't know whether it is  
13 just the small, triglyceride-rich lipoproteins in the  
14 fasting plasma, or in the post-prandial plasma that  
15 are the atherogenic things. We certainly have  
16 evidence to suggest they are both pathophysiologically  
17 and epidemiologically.

18 But they also mark the presence of other  
19 things which can be atherogenic, such as a low HDL,  
20 small dense LDL, coagulation abnormalities, and the  
21 presence of insulin resistance and hyperinsulinemia.

22 But it probably doesn't matter as I say,

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1 because reducing plasma triglyceride not only reduces  
2 the lipoproteins, but reverses all of the changes that  
3 one sees in these marker defects as well.

4 What about the situation as far as the  
5 treatment of hypertriglyceridemia is concerned? The  
6 first hint that this was beneficial came from the  
7 Stockholm Secondary Intervention Study, a study which  
8 used clofibrate and niacin to reduce plasma  
9 triglycerides and found a beneficial effect on  
10 myocardial infarc survivors.

11 In another, more recent study from Stockholm  
12 published in 1996, the BECAIT Study, a group of young,  
13 male myocardial infarc survivors were treated either  
14 with placebo or bezafibrate -- a fibric acid  
15 derivative drug which is shown to reduce triglyceride  
16 and increase HDL.

17 It was initially designed to be an  
18 angiographic study and what one can see is, given the  
19 placebo group there was a greater reduction in the  
20 minimal lumen diameter than there was in the  
21 bezafibrate-treated group.

22 Although it was not initially thought that

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1 it would be powered any clinical events, the  
2 surprising but also gratifying thing is that there was  
3 in fact, a reduction in clinical events in these  
4 individuals who were treated with bezafibrate.

5 The situation in diabetes is at an even more  
6 infantile stage of the game. We are currently  
7 conducting a clinical trial, which is an angiographic  
8 trial, looking at whether reducing plasma in lipids  
9 with people with diabetes will reduce their risk of  
10 coronary disease.

11 That is a study which should be completed  
12 and out within the next year-and-a-half. In that  
13 interval of time the one hint that we have was just  
14 very recently published from London, the Sencap Study;  
15 a study which Elkeles and his colleagues undertook,  
16 treating people -- and pardon me but my slide maker  
17 cut off the top line here -- treating people who had  
18 type 2 diabetes, with bezafibrate or placebo.

19 And what one can see is that there was a  
20 reduction in plasma triglyceride in the bezafibrate-  
21 treated group; not a major change in LDL but an  
22 increase in HDL. The study initially examined carotid

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1 intermedial thickness and found no difference in that.

2 But looking at coronary events which would  
3 either confirm myocardial infarction or ischemic  
4 changes taken to be coronary events, there was a  
5 reduction in coronary events that occurred through the  
6 study in those who are treated with bezafibrate.

7 So that there are hints as well that  
8 specifically in the diabetic population there will be  
9 a benefit to reducing plasma triglycerides.

10 Thus, in summary I think that we can say  
11 that there is an increasing body of evidence that  
12 hypertriglyceridemia is a risk for coronary artery  
13 disease -- at least marks a risk even if the  
14 triglyceride-rich glycoproteins themselves are not;  
15 that it is a risk for coronary disease in those with  
16 diabetes.

17 That in the general population we're using,  
18 plasma triglycerides is now getting increasing support  
19 to show that it will reduce coronary events, and that  
20 there are hints emerging, and these will come more  
21 strongly hopefully, in the future, to demonstrate that  
22 this applies to diabetic individuals as well as to

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1 those without.

2 Thank you very much.

3 CHAIRMAN SHERWIN: Thank you. I don't see  
4 any comments. What I would suggest is we have a break  
5 now I think all of us could use. We'll start promptly  
6 at 11 o'clock.

7 (Whereupon, the foregoing matter went  
8 off the record at 10:45 a.m. and went  
9 back on the record at 11:02 a.m.)

10 CHAIRMAN SHERWIN: I think we can now  
11 resume, and the focus now will be on the safety data.  
12 Dr. Paul.

13 DR. PAUL: Thank you, Dr. Sherwin. I know  
14 that we're running a little bit behind at the present  
15 time. I'll try to speed things up but I don't want to  
16 go too fast because we believe that safety is a very  
17 important part of the balance that makes up the total  
18 assessment and benefit to risk.

19 As we all are acquainted with the active  
20 ingredient, bromocriptine has been with us for about  
21 two decades, therefore, it's been well characterized  
22 as far as its safety profile. What I'm speaking to

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1 here primarily is that safety profile really driven by  
2 the central mechanism of action for over the 20 years  
3 of its use.

4           Indeed in our Ergocet™ studies we will show  
5 you that that safety profile has more or less stayed  
6 in agreement with that historically shown for the  
7 product; that these adverse events in our studies  
8 tended to occur fairly early on in the course of the  
9 treatment period. They were mild or moderate, and  
10 very transient in nature.

11           A little bit about the marketing history of  
12 the active ingredient itself. As you know this was  
13 introduced in the United Kingdom 1976, later in the  
14 United States, for a myriad of hyperprolactinemic  
15 disorders.

16           Current indications are for  
17 hyperprolactinemia disorders covering a broad range of  
18 disorders. Doses of 5 to 7.5 milligrams a day are  
19 commonly given for those. In the small group of  
20 acromegaliacs doses are a little higher, going up to  
21 20, 30 kilograms a day. And finally, as a treatment  
22 for Parkinson's Disease much higher doses are given

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1 and they're given in divided doses over the entire  
2 day.

3 Just to give you a reference point,  
4 historically, of the frequency of the most commonly  
5 reported adverse events -- those events again, that  
6 are centrally caused. Nausea appears basically on the  
7 top of the list each time we look at any specific  
8 database.

9 In the hyperprolactinemic disorders at the  
10 lower doses even, you see almost a 50 percent  
11 incidence of nausea on the package insert labels of  
12 those commercially available products; headache and  
13 dizziness. The same sort of pattern appears -- this  
14 centrally mediated, adverse event -- nausea, some  
15 constipation, the mechanistic expression of the action  
16 of the drug that you've heard already, producing some  
17 hypertension in this population.

18 And of course in Parkinson's Disease at the  
19 higher dose they have had reports of hallucinations  
20 and confusion at the very high doses of bromocriptine.

21 What I will review primarily for you today  
22 is our own database, but we have looked indeed, very

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1 diligently, at the FDA's spontaneous adverse event  
2 report system. As you know, about 95 percent of those  
3 reports are reported by the sponsors.

4           Anyway, the World Health Organization also  
5 maintains a spontaneous reporting system, albeit a  
6 myriad of confounders and understanding what the data  
7 is, but still they were numbers here that we looked  
8 at. And of course, we did look into the database of  
9 the comprehensive literature search because of the  
10 history of this drug.

11           Before I get into our own database I do want  
12 to mention to you that we're very cognizant of course,  
13 of events that occurred in the late '80s and early  
14 '90s, in the small, select population of women who  
15 were post-partum and suffered some untoward effects  
16 from the use of low doses of bromocriptine.

17           These young women were characteristically 25  
18 years of age. They took low dose of 2.5 milligrams  
19 b.i.d. as we all know, and had some reactions that  
20 were absolutely contrary to the expected actions of  
21 the drug. That was recognized; several case reports  
22 were reported to the agency; there was a

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1 recommendation to the sponsor company to withdraw the  
2 indication; and it was voluntarily, subsequently  
3 withdrawn -- I believe in 1994.

4 Let me now address the data that we  
5 collected in our own studies. In defining the patient  
6 population again, I think it's very useful to know  
7 what exposure we're talking about. Of the 1,096  
8 patients of which we collected the safety data from,  
9 894 were exposed to Ergocet™, 416 in the placebo  
10 population.

11 As we had open label extensions to each of  
12 the three controlled studies, those patients who were  
13 formerly placebo were crossed over, and that  
14 represents this 217 patients to the Ergocet™  
15 population.

16 To give you an idea of the actual exposure  
17 with our formulation, we took a summary of the patient  
18 years collected from the adjunctive, monotherapy,  
19 single and multiple dose studies and the core Phase 2  
20 studies, and we came out with a total exposure of 372  
21 patient year exposures.

22 That should be in addition to the millions

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1 of prescriptions that have been written for  
2 bromocriptine which have resulted with really no  
3 intense mathematical projection in virtually thousands  
4 of patient years on top of that.

5 The duration of exposure in our own program  
6 -- this is carried out the XX studies, which means  
7 that we have a 6-month as you know, control period, in  
8 which we looked at the product with the control  
9 comparator -- either placebo or the active comparator,  
10 sulfonylureas -- and we extended those studies out an  
11 additional two periods of time in an open label  
12 fashion, and each of these XXs represents an  
13 additional six months of extension.

14 Well, as you can see here, we do have a  
15 number of patients that went out past the year, and  
16 we'll be discussing that a little bit more in detail.

17 What was the adverse event profile? If we  
18 look here at the adjunctive study which must be broken  
19 out in the monotherapy study, it is because there is  
20 a different expected profile with patients who are on  
21 sulfonylurea treatment.

22 One can see right away that in accordance

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1 with the known history, the historical safety  
2 database, the centrally driven adverse events once  
3 again occurred with the highest frequency -- in both  
4 the adjunctive therapy and in the monotherapy study.

5 If you take nausea as an example of these  
6 centrally acting adverse events -- and I might add in  
7 passing, we looked at the top five adverse events in  
8 the same way we looked at nausea to try to  
9 characterize again, when did these events occur, how  
10 long did they last, what was the severity of these  
11 events, and do they keep coming back with therapy?

12 Well, what we did for you, to give you an  
13 illustration of that, the time of first occurrence is  
14 certainly grouped up here in the beginning of therapy  
15 where you have the number of patients here reporting  
16 the highest number of events early on the course of  
17 therapy.

18 The duration of nausea on the X-axis here --  
19 that's zero to seven days and these are the number of  
20 days thereafter -- you will notice here on the X-axis  
21 there's a break here in the line because of course  
22 there's a lumping into with a much larger disbursement

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1 of days, the number of events. And here we have the  
2 number of occurrences in nausea here.

3 And again, these events tend to occur no  
4 longer than usually part of a day, an early morning,  
5 and went away. They were transient in nature. The  
6 case report form did not give us the actual  
7 specificity of the minutes that the actual adverse  
8 event ended, but again, they did indeed, group mostly  
9 around a very short duration of time.

10 When we look at these subgroups -- and this  
11 is an important aspect of looking at any safety  
12 database for sex, race, and age, we found that women  
13 tended to report more headache, vomiting and nausea  
14 than the men in the controlled studies. That was  
15 regardless of the treatment group, and that the  
16 Ergocet™ rates were higher than that of placebo.

17 With regard to race, we didn't find any  
18 statistically significant differences between the  
19 groups, and the frequency of constipation, nausea, and  
20 dizziness, had a slight increase in older patients  
21 over the age of 65 on Ergocet™ therapy.

22 For hypoglycemia we took a look at this

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1 because in all drugs it affects glycemic control --  
2 that's an obvious question to look at -- and in our  
3 studies one must understand that all events were based  
4 on patient-reported symptomatology.

5 So we're talking here about symptomatic  
6 hypoglycemia, which is a very large sort of term in  
7 which you can fold into several different types of  
8 adverse events from a subjective basis.

9 The majority of these reports were reported  
10 as mild. There were 75 percent of them; there were no  
11 serious, adverse events among any of the patients in  
12 any of the studies. There were no withdrawals from  
13 studies driven by so-called hypoglycemia, and  
14 absolutely no confirmed second person intervention.

15 The most serious reported hypoglycemia,  
16 which is not a serious adverse event but classified on  
17 the mild, moderate, severe type classification of an  
18 adverse event, was treated with a piece of candy and  
19 resolved.

20 However, we did look at it in a detailed  
21 fashion. And what we saw in K and L, which are the  
22 adjunctive studies combined, we had a rate of 8.6

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1       versus 5.5 in the placebo population; not  
2       statistically significant.

3               In the monotherapy study the numbers were  
4       even lower: 2.5 rate to a 1.3 -- again, not arriving  
5       at any statistical significance. Combining all the  
6       studies, again we did the same comparison and there  
7       was no statistical significance.

8               So our conclusions for symptomatic  
9       hypoglycemia was that the rates of Ergocet™-treated  
10      patients were no different from the placebo-treated  
11      patients when one used the combined studies from the  
12      studies K and L combined, or K, L, and M combined.

13              What about the vital signs,  
14      electrocardiograms, and laboratory determinations?  
15      For blood pressure, which is something that we really  
16      looked at in detail, what we found was that the  
17      excursions from the baseline either up or down for  
18      systolic blood pressure, did not exceed on a mean  
19      basis, more than five millimeters of mercury.

20              There were no clinically meaningful changes  
21      in the heart rates, and the mean changes in the  
22      cardiac parameters from the electrocardiograms that we

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1 measured show no clinically meaningful changes.

2 In our clinical laboratory assessments in  
3 looking at all the assessments -- other than of  
4 course, the efficacy parameters which we did see some  
5 nice changes in which you've seen already -- two  
6 patients did have elevations in liver function tests.

7 No other patients experienced a significant  
8 shift in any of the other laboratory parameters.  
9 Let's take a look at the two patients because it was  
10 important for us to understand what happened to them.

11 In study L, adjunctive study, we found that  
12 one patient had an increase of LLTs around the 16th  
13 week of therapy. They had never reported a prior  
14 event. They were on the maximal dose for the study --  
15 4.8 milligrams.

16 The relation, whether or not the  
17 investigator could relate the incidents to study drug  
18 or not gave an unknown mark on the EK report form. Of  
19 course the intensity was marked as severe; the action  
20 at the site was to discontinue the patient immediately  
21 and follow the patient very closely.

22 That patient however, was referred to a

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1 center for complete workup, underwent ultrasonography  
2 to the liver. A fatty liver was found in  
3 ultrasonography. Attempts thereafter were made to  
4 contact institution and patient. These attempts  
5 failed. The patient was lost to follow-up after  
6 several attempts.

7 The second patient also in adjunctive  
8 therapy, at week-24 with no prior event, at 4.8  
9 milligrams, with a possible relation to study drug.  
10 The same thing for intensity; was rated on the EK  
11 report form as severe, to discontinue the patient  
12 immediately.

13 The patient was followed until the event  
14 resolved and the event resolved in a matter of four  
15 weeks. The LLTs fell to normal. There was a negative  
16 hepatitis screen and a negative ultrasound for that  
17 patient.

18 For study discontinuations what we had is,  
19 about 75 percent of the patients completed the  
20 studies, in all three studies combined. Adverse  
21 events accounted for 12.7 percent of the reasons of  
22 discontinuations, versus 3.3 for the placebo.

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1           The most common adverse event that drew the  
2 patients to discontinue from study, again was  
3 consistent with what we saw historically for adverse  
4 events: nausea, dizziness, dyspepsia, headache. The  
5 rates again, very, very small throughout.

6           For study M the same recurring theme. The  
7 nausea causing a very small percentage of the 82  
8 discontinued.

9           Serious adverse events. For the controlled  
10 studies, four percent of the 324 Ergocet™-treated  
11 patients had serious adverse events reported and  
12 reported to the agency, versus 3.3 percent of the 329  
13 placebo-treated patients.

14           In the uncontrolled extensions from 24 to 48  
15 weeks, this rose to 6.8 percent for crossover group --  
16 that was the group that I had described to you  
17 earlier; those are the non-placebo and then crossing  
18 over in the open label extensions -- versus 6.8  
19 percent for the Ergocet™ who had been continuing out.

20           And the same held true as you moved out in  
21 48 weeks, dropping a little bit off -- 5.8 percent  
22 versus 6.3. We think that the extension in time

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1 really is a driver of the small increments, if you  
2 will, in the frequency of adverse events.

3 In other words, as one moves out in time in  
4 continuum in this population, the likelihood of seeing  
5 an adverse event would tend to rise.

6 What about the serious adverse events? The  
7 most common was myocardial infarction. We had three  
8 myocardial infarcs in the control period of the study,  
9 versus one infarc in the placebo group.

10 In the extension studies, five other  
11 myocardial infarcs occurred, and we'll talk about that  
12 in some detail in just a moment. And as you can see  
13 there was a very low percentage there on out of the  
14 other listed, serious adverse events.

15 The safety conclusions overall are  
16 consistent historically with the safety conclusions of  
17 the active ingredient. That has been well  
18 characterized. The majority of these adverse events  
19 were mild, moderate, or transient, and the majority  
20 were not serious.

21 What I'd like to do, because any signal of  
22 any event we looked into very carefully. We are

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1 concerned about the safety of our patients who take  
2 our drugs. And so in seeing the cardiovascular issues  
3 as far as having a myocardial -- even one myocardial  
4 infarction occurred -- we wanted to make sure that  
5 this was something that wasn't a characteristic  
6 problem of the drug.

7 Indeed, we found that to be the case, and to  
8 explore that with you, Marcia Testa has joined us.  
9 Dr. Testa is from the Harvard Public Health -- School  
10 of Public Health. And she will take us through some  
11 analysis which will put into perspective these  
12 cardiovascular events.

13 Marcia.

14 DR. TESTA: The first thing that I did, I  
15 was asked to conduct an independent evaluation of the  
16 incidence of cardiovascular adverse events, and as you  
17 know, coronary heart disease is the leading cause of  
18 death of diabetes, and certainly people with diabetes  
19 are at increased risk for cardiovascular events.

20 We know this from the NHANES database  
21 starting with NHANES-1 and now with NHANES-3.  
22 Patients, diabetic males, have an increased risk of

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1 diabetes -- up to four-fold -- and for women up to  
2 three-fold.

3 So the idea that you're seeing numbers of  
4 people with cardiovascular adverse events is not odd  
5 in this case. The question that I wanted to answer  
6 was, is there an increased risk due to the addition of  
7 Ergocet™ on top of this already increased risk for  
8 patients with diabetes?

9 The first thing that I looked at was the  
10 actual data at hand, the controlled studies, which has  
11 been reviewed for you for K, L, and M. And this is  
12 where you really have the only comparison data to  
13 placebo, and then looked at the uncontrolled  
14 extensions.

15 If we convert the events that we see to the  
16 incident rate per year which controls for the degree  
17 of exposure, the incident rates we're talking about --  
18 .097 to .073 -- this represents 12 cases out of 312  
19 patients; this represents ten cases out of 319  
20 patients.

21 Then we can look at this. This is not a  
22 large difference, it's not statistically significant.

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1 If we break this down into subgroups, take serious  
2 cardiovascular events as a subgroup, we have .03  
3 versus .022 -- again, four cases versus three.

4 Here if we look at myocardial infarctions we  
5 have an incident rate of .024 versus .007. And it's  
6 here when you hit the actual limit of zero that you're  
7 getting a relative risk. This relative risk ratio is  
8 2.9 and it has a lower limit of .49 and an upper limit  
9 of 65.

10 This means, sort of like a car mechanic  
11 giving an you estimate for fixing your car, saying it  
12 ranges anywhere between 29 and 29,000. This is not a  
13 very stable estimate and because of that, when you hit  
14 the bottom where this is based upon one case and this  
15 is based upon three cases, these type of comparisons  
16 are not really very useful.

17 If we look at the extended data we're  
18 getting better precision here in our Ergocet<sup>TM</sup>-treated  
19 group. And if we look at this, the length of time has  
20 now extended by three, and we have the same incident  
21 rate patterns.

22 We have now 35 cases. The length of time is

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1 three times which is just about three times 12. Here  
2 now we have 14 cases, about three times four; again,  
3 consistent. And here we have eight cases; again  
4 consistent. About three times three, which is about  
5 three times over the exposure which is three times as  
6 long. Which is what you'd like to see because you  
7 don't want to see an increase in exposure over time.

8 In other words, the risk is not accumulating  
9 over time. Here of course, we don't have the same  
10 data for comparison this relative risk ration than  
11 it's still based upon a per comparison here.  
12 Something that's based upon one or zero is really  
13 worthless in drawing any conclusions about increased  
14 risk.

15 So from that point we have to look at  
16 another alternative for decision-making. Since the  
17 rates of Ergocet<sup>TM</sup>-treated patients were not  
18 statistically significant different from placebo-  
19 treated patients using the combined data from the K,  
20 L, and M studies, we're saying from the clinical data  
21 we can't in fact, see any increased risk.

22 But then the question comes up, our

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1 comparator group doesn't have enough power to really  
2 focus on knowing whether that rate of .022 -- which is  
3 about two events for every 100 patients you follow for  
4 a year -- where does that stand relative to patients  
5 with similar characteristics in diabetes?

6 So to answer that particular question we had  
7 to go to a large reference database. Now, in  
8 existence right now the only incidence data that is  
9 available for people is NHANES.

10 Fortunately however, I've been working for  
11 two years with a very large New England insuring  
12 database where we have extracted all people who have  
13 been on oral hypoglycemic agents between the periods  
14 of July 1991 and 1996.

15 This is a large, link claims database having  
16 all prescription medications, all hospitalizations,  
17 and all business to the physicians, in one big record  
18 format. It includes 18,847 patients with Type 2  
19 diabetes, totalling 70,695 person-years of follow-up.

20 The group is very similar to the controlled  
21 clinical trials groups that we have in these studies.  
22 The average age is 52 years. We have in this database

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1 more females than was in the controlled studies,  
2 stacking the deck against Ergocet™ which is a safe  
3 thing to do when you're doing safety analysis.

4 About 67 percent of them were on glyburide.  
5 We eliminated insulin users only, so we eliminate that  
6 from our group. And we eliminated persons under the  
7 age of 30 -- again consistent with the group in which  
8 the clinical trials were done.

9 We found 2,988 hospitalizations for an MI --  
10 which is an ICD codes; all the 410s -- point-zero to  
11 .9. That represents again, 70,695 years of person  
12 follow-ups. This is an event rate of .042 per year  
13 which is about 4.2 per 100 patients followed for a  
14 year.

15 And when you're dealing with such large  
16 databases like this you don't need statistics anymore  
17 because basically the confidence interval goes from  
18 .041 to .044. So that's our reference value; what is  
19 the usual situation -- in a number of people in this  
20 large population -- what is their incidence of MI?

21 Remembering, going back, the Ergocet™  
22 comparison had eight MI events -- .022. And if we

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1 compute the confidence interval around that it goes  
2 from .009 to .042.

3 Now, even with more males in this population  
4 for that events, is about half -- running  
5 statistically lower in favor of Ergocet™, but not to  
6 say that it's protective because you know when you  
7 enter people into trials there's a number of exclusion  
8 criteria that you have and a number of other things.  
9 So where you want to see this reference point to  
10 assure you of a safe, profile, is much lower. Indeed,  
11 here it's about half.

12 However, being a conservative individual  
13 when it comes to pharmaco-epidemiology and safety, I  
14 would like to see the worst-case scenario played out  
15 in this. So the next slide is an example of one of  
16 the worst-case scenarios.

17 And that says, let us assume that an event  
18 rate that we have in these trials of .022 -- in fact,  
19 we will assume that that upper confidence limit is  
20 actually the real value. Now, there's a two-and-a-  
21 half percent chance that it will be the real value;  
22 it's usually sitting at the mean.

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1                   But let's put it all the way up to as far as  
2                   it will go given our estimates, and let's compare it.  
3                   At that time we have .03 for Ergocet<sup>TM</sup> versus .042 --  
4                   virtually identical. So even pushing it up to its  
5                   upper limit, they sit on top of each other.

6                   Another way to look at this would be to say  
7                   that, well maybe our database that we have, in fact,  
8                   there's a problem -- so if we can go to the next slide  
9                   -- there's a problem. Let's say we only counted two  
10                  admissions for every one MI. Say we thought for some  
11                  reason people were being admitted twice if there were  
12                  two admissions for only one event.

13                  If we worked the sensitivity analysis that  
14                  way, we again now get .02 events rate per year in our  
15                  reference database, compared to .022 events per year  
16                  in our clinical control trials.

17                  Again, absolutely no difference here in the  
18                  next slide. So that the conclusion here is that if  
19                  you look at the raw comparison, the Ergocet<sup>TM</sup> MI rates  
20                  were lower by nearly half, then the reference  
21                  population of persons with Type 2 diabetes using oral  
22                  agents, .022 versus .042, P equals .04.

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1           Using two sensitivity analysis posing the  
2 worst possible scenario for Ergocet™ -- in other  
3 words, using the upper 95 percent limit of the  
4 observed Ergocet™ MI rate and secondly, counting two  
5 admissions for one event in the reference -- neither  
6 of these support an hypothesis of increased risk due  
7 to Ergocet™ treatment.

8           So since the observed MI rates were  
9 comparable or lower than the reference population of  
10 type 2 diabetes and similar to placebo in all clinical  
11 studies, I concluded that there was no evidence to  
12 support a causal association between Ergocet™ and an  
13 increased risk above the endemic rate in patients with  
14 diabetes for cardiovascular adverse events.

15           And right now I just -- that concludes my  
16 statements -- but right now I'd like to introduce Dr.  
17 Bertrand Pitt who's a professor of Medicine in the  
18 Division of Cardiology at the University of Michigan,  
19 and has been on advisory committees and the steer of  
20 a committee in the cardiovascular area, to comment on  
21 the actual case studies.

22           DR. PITT: Thank you very much. I'll be

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1 very brief. Obviously, the number of cases of  
2 myocardial infarction are really too few to comment on  
3 any risk or benefit.

4 I did however, review the individual case  
5 histories of all the patients with myocardial  
6 infarction to look for some pattern to give me some  
7 insight as to whether there was a particular mechanism  
8 or type of infarction or whether we were dealing with  
9 any relation to hypotension spasm.

10 And when we looked through the individual  
11 case histories it's really pretty clear that this is  
12 what you would expect in a group of patients with  
13 diabetes. Many of them had extensive coronary  
14 disease, previous bioplast graft surgery, or when they  
15 had their infarc they went to angiography and then had  
16 extensive disease and underwent PTCA.

17 I really couldn't discern any particular  
18 pattern, and this is what I would expect looking at  
19 both the extension patients as well as the randomized  
20 patients from our ordinary population with coronary  
21 disease and diabetes. Thank you.

22 DR. PAUL: Well, almost in conclusion -- and

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1 Dr. Sherwin, we are concluding right now -- but almost  
2 in conclusion we have shown, I believe dramatically,  
3 that Ergocet™ is indeed, effective in the population  
4 of which it's intended for use -- in the Type 2  
5 diabetic person.

6 We have shown data to show that there's been  
7 a reduction -- nice reductions in glycemia, in  
8 triglycerides, and the high levels of free fatty acids  
9 which drive those high levels of triglycerides. We  
10 have shown that Ergocet™ is safe in the intended  
11 population.

12 We have characterized the safety profile;  
13 that safety profile is almost exactly what we would  
14 expect from the historical knowledge that we have  
15 gained from understanding those 20 years of  
16 experience. And that the therapeutic value is  
17 indicated in our opinion, by a positive, benefit-to-  
18 risk profile.

19 So in conclusion, we have presented evidence  
20 which we believe supports this positive benefit-to-  
21 risk profile for Ergocet™, a novel, centrally acting,  
22 therapeutic approach to the treatment of Type 2

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1 diabetes.

2 Our claim platform which we are seeking,  
3 there are indications in the population of those Type  
4 2 diabetes treated with sufonylureas, and as a  
5 monotherapy alone in that same population.

6 Thank you very much.

7 CHAIRMAN SHERWIN: Thank you, Dr. Paul. I  
8 think we should hold off on questions and begin with  
9 the FDA presentation. Unless there's something  
10 burning. We will get into things in the afternoon.

11 So our next speaker representing the FDA is  
12 Alexander Fleming.

13 DR. FLEMING: Thank you, Dr. Sherwin, and  
14 members of the committee. Thank you very much, first  
15 of all, for your being here for yet another 3-day  
16 meeting. And certainly the FDA has gotten its money's  
17 worth from this committee. We appreciate the very  
18 hard work and I thank Ergo for their very good  
19 presentation. It's been very interesting.

20 I also -- and this sounds like the academy  
21 words, I know -- but I want to thank the reviewers on  
22 the review team. First, Dr. John Guerigurian who's

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1 the primary, clinical reviewer; Dr. Ron Steigerwalt,  
2 the pharmacologist and our team leader for  
3 pharmacology; Dr. Javier Ysern who is the chemist; and  
4 Dr. Rod Shore who is our pharmacokineticist.

5 And special thanks to, as it was mentioned  
6 earlier, Mike Johnston, who is an outstanding project  
7 manager. Unfortunately, we're losing him to another  
8 opportunity within the FDA, but he has been truly a  
9 sterling example of project managers for the agency.

10 Now, if I can have the next slide. We will  
11 have a relatively short presentation. You'll hear  
12 first from me, some general regulatory considerations  
13 that I hope you'll continue to keep in mind. And I'll  
14 give you a sense of our approach to evaluating  
15 efficacy in this particular case.

16 I will be followed by Dr. Pian with a  
17 statistical evaluation of efficacy, and then I will  
18 return to talk briefly about some clinical  
19 considerations, including the safety review.

20 Now, I just want to point out that we  
21 generally evaluate efficacy by estimating the  
22 treatment effect using the intent-to-treat population.

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1 The treatment effect is simply to find -- is the  
2 response of the experimental drug minus the response  
3 of the placebo group, with adjustment if necessary,  
4 for any baseline differences.

5 Now, the significance of the treatment  
6 effect particularly when a surrogate endpoint is  
7 involved, as in this case -- even though this is a  
8 well substantiated surrogate endpoint -- requires  
9 clinical judgment. And that is why you are here  
10 today.

11 Finally, the provability of a therapy is  
12 ultimately based on the relationship between benefits  
13 and risk.

14 Now, we will certainly agree that glycemic  
15 control as reflected by glycated hemoglobin levels, is  
16 the well-validated surrogate for microvascular  
17 complications outcomes. the improvement in HbA1c  
18 appears to be proportional to benefit. In fact, there  
19 may even be a threshold effect whereby relatively  
20 small changes in certain regions of the hemoglobin A1c  
21 concentration occur, result in even larger clinical  
22 benefits.

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1           And I would also say that no minimum level  
2 of glycated hemoglobin improvement has been  
3 established that represents a lack of clinical  
4 significance.

5           Just a few words about the responder  
6 analysis, and you've already heard that presentation  
7 from the sponsor. There's nothing wrong with using a  
8 responder analysis, and in fact it is often  
9 appropriately used when there is a complex situation  
10 where several variables are having to be included at  
11 the same time.

12           In this case let me stress that it is a  
13 useful procedure but not so much to evaluate the  
14 efficacy of the drug but as a means of advising  
15 clinicians about how to best select patients. And so  
16 that is that appropriate use of the responder analysis  
17 in this case.

18           And you should as a committee, emphasize the  
19 intent-to-treat results in your considerations,  
20 bearing in mind that by enriching the population in  
21 which you would expect a better response but could  
22 represent an additional advance in the use of the

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1 drug, that this is at the level of drug product  
2 labeling and not at regulatory decision.

3 All right, now I'll introduce Dr. Pian who  
4 will give you a brief biostatistical presentation.

5 DR. PIAN: Thank you, Dr. Fleming. My  
6 discussion is on those three Phase 3 trials of  
7 bromocriptine for Type 2 obese diabetic patients. I  
8 will (unintelligible) the sponsors for regional  
9 training of Ergocet™ throughout.

10 All three trials were conducted in the  
11 United States. It all started in January 1995 and  
12 completed sometime during 1996. The duration of each  
13 trial was six months. There was a 2-week screening  
14 period.

15 Patients in studies K and L received stable,  
16 concomitant low doses of sulfonylurea, oral  
17 hypoglycemic agents. The patients in study M received  
18 Ergocet™ as monotherapy. All trials patients were on  
19 an ADA weight maintenance diet which was an  
20 individualized diet.

21 The 6-week titration started patient with  
22 one tablet per day for a week, then at increments of

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1 one tablet per week if the drug is tolerated, up to  
2 six tablets per day at week-6. In order to stay in  
3 the trial patients needed to tolerate at least a  
4 dosage of two tablets per day.

5 The study drug administration was at 8 a.m.,  
6 plus or minus 30 minutes, with food. In the protocol,  
7 the primary objective was to demonstrate a clinical  
8 and significant difference which is defined as a  
9 reduction of 1.0 percent or greater, in the level of  
10 hemoglobin A1c.

11 Subjects treated with bromocriptine plus an  
12 ADA weight maintenance diet, when compared to a  
13 placebo-treated group on a weight maintenance diet.  
14 The three pertinent inclusion criteria were HbA1c, BMI  
15 -- that's body mass index -- and prolactin profile.

16 Studies K and L enrolled patients with a  
17 baseline HbA1c between 7.8 to 12.5 percent. For the  
18 monotherapy trial M, it was lower, at 7.5 to 11  
19 percent. The BMI criteria was 26 to 40 for men, and  
20 28 to 40 for women.

21 Patients with a normal prolactin profile  
22 were excluded from the trial. Also, patients had to

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1 sleep at least five hours between 10 p.m. and 8 a.m.

2 For the disposition of patients, studies K  
3 and L randomized around 120-some patients in each  
4 treatment group. For study M it was around 80 per  
5 treatment group. The completion rates were about 75  
6 percent for all the Ergocet™-treated patients.

7 For placebo-treated patients it was higher,  
8 at 86 percent for studies K and L, and 78 percent for  
9 study M. The lower completion rate in the Ergocet™  
10 group were primarily due to dropout from the adverse  
11 events.

12 As we know that our trial patients were  
13 under a forced titration scheme, this slide shows the  
14 percentage of patients by the final dosages. For all  
15 three trials, the distribution was similar. It was  
16 around 75 percent for the Ergocet™ patients compared  
17 to 94 percent of the placebo patients that reached the  
18 maximum dose of six tablets per day.

19 For the primary efficacy variable, it was  
20 HbA1c, and the primary analysis was on the outcome  
21 variable change from baseline to week-24. The  
22 endpoint analysis was performed on the last

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1 observation carried forward -- that is dataset of the  
2 intent-to-treat population -- while the week-24  
3 analysis was on the observed cases of the ITT  
4 population.

5 The difference of the two treatment groups  
6 was compared. This graph on the left shows the mean  
7 HbA1c for study K over time. That is for the observed  
8 cases dataset. And the final point represents the  
9 means at week-24 using the last observation carried  
10 forward for the non-completers.

11 As we can see, the Ergocet<sup>TM</sup>-treated  
12 patients in the beginning has a sharper decrease than  
13 placebo in HbA1c. The decline leveled off at week-12,  
14 then it started to rise, while the placebo started its  
15 rise around week-8, steadily to the end of trial.

16 On the right side is the responding fasting  
17 plasma glucose over time, which was the secondary  
18 efficacy variable. It was measured at only three  
19 timepoints, but from these three points we can tell  
20 its decrease and increase were similar to HbA1c.

21 The next is the similar graph for study L;  
22 similar pattern as study K. Sharp decrease in the

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1 beginning and increase after week-12 for Ergocet™.  
2 And that is for study M. The baseline, HbA1c is a  
3 little lower than it was in studies K and L, so the  
4 similar pattern is observed -- similar to the other  
5 two studies.

6 This slide shows the change from baseline in  
7 HbA1c for all three studies. The X-axis starts as a  
8 change from baseline to week-4 after week-24 for the  
9 observed cases dataset, and at endpoint for the LOCF  
10 dataset.

11 At week-24 all placebo-treated groups had an  
12 increase in HbA1c -- that is, a positive change --  
13 while the changing HbA1c in the Ergocet™ groups was  
14 zero in study K, or negative for studies L and M. The  
15 differences between the Ergocet™ and placebo groups  
16 were all statistically significant.

17 This slide shows the treatment difference  
18 between treatment groups in change from baseline to  
19 week-24 with their confidence intervals at week-24 for  
20 the endpoint -- that's LOCF -- and the week-24 --  
21 that's observed cases of relation analysis.

22 The P value that's less than .01 pertain to

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1 all four analyses for studies K and L. The other two  
2 P values are related to study M analysis. For  
3 endpoint, the treatment differences were -.49, -.59,  
4 and -.42 for the three studies.

5 For week-24 the differences were -.48, -.62,  
6 and -.54, respectively, for studies K, L, and M. For  
7 the sustainability of Ergocet™ during the study, the  
8 FDA performed a repeated measurements analysis on data  
9 from week-12 to week-24.

10 The results show the effect is sustained  
11 from week-12 to the end of the trial, as the previous  
12 graph shows. The two lines are reasonably parallel  
13 after week-12.

14 So in conclusion, the two adjunctive therapy  
15 trials, K and L, as well as the monotherapy trial, M,  
16 all showed statistically significant differences  
17 between Ergocet™ and the placebo in change of HbA1c  
18 from baseline to week-24.

19 The repeated measurements analysis showed  
20 that the effect of Ergocet™ is sustained from week-12  
21 to week-24. Thank you.

22 DR. FLEMING: Thank you, Lee. Let me just

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1 say as I get started, that I noticed that the  
2 committee members have been provided with handouts of  
3 our presentation. Unfortunately you have a slightly  
4 older version than the one that you're going to see.  
5 It differs only in the last several slides so it's not  
6 a major thing.

7 If I could have the next slide and go on to  
8 the next one. Let me just start by summarizing the  
9 treatment effects here. As you've heard, we have seen  
10 some improvement in glycemic control as reflected by  
11 glycated hemoglobin, and these results are highly  
12 statistically significant.

13 But there is certainly, more than just  
14 looking at the bottom line here. Let's look at a few  
15 considerations related to efficacy that will be seen  
16 or summarized on the next slide.

17 First, just a few comments about study  
18 conduct and then we'll talk about the composition of  
19 the treatment effect, and the effect on weight. I  
20 might also acknowledge that there certainly is some  
21 tantalizing data about beneficial effects on lipids,  
22 but I will not cover that topic any further. I think

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1 it will though, be a very useful point of discussion  
2 this afternoon.

3 And then we'll talk about the durability of  
4 the treatment effect with the available data that we  
5 have.

6 Now, on conduct of the study, first of all  
7 there were no statistically significant baseline  
8 differences between treatment groups. There were some  
9 trends which I do not believe account for the results,  
10 particularly in duration of diabetes among the  
11 different experimental groups.

12 And also there is a slight difference in the  
13 number of patients who make it to the point that they  
14 are considered for ITT -- for the intent-to-treat  
15 analysis. That is to say that a few were screened out  
16 and not surprisingly so because of the nausea  
17 associated with the drug before they actually got to  
18 that point.

19 There could be some discussion about whether  
20 ITT should begin with the first treatment or at a  
21 point defined beyond initial treatment.

22 It's interesting that the prolactin

1 criterion -- or criteria, actually -- did not screen  
2 out any patients. I think there may have been one or  
3 two patients who were screened out, but essentially  
4 all these patients that were screened on the basis --  
5 with prolactin levels -- entered the study without  
6 having failed the criteria for prolactin plasma  
7 levels.

8 Let me again just remind you that study M  
9 tested only patients that were naive to sulfonylurea  
10 therapy, and in fact, this seems to be the case; that  
11 virtually every patient had never been on sulfonylurea  
12 therapy or at least in one or two cases, it has been  
13 at a very distant point in history.

14 There was of course, a very high dropout  
15 rate in the treatment group due to the well-known  
16 effect of the drug, but I don't see that this has  
17 resulted in any apparent systematic bias in favor of  
18 the drug as the result of the imbalance in completers  
19 in the study.

20 Now, let's go on to look at the components  
21 of the treatment effect. Here in study K you can see  
22 that the treatment effect is almost entirely due to

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1 the deterioration of the placebo group from baseline.

2 And if we go to study L we'll see that  
3 fortunately, there seems to be a greater contribution  
4 in absolute decline from baseline associated with  
5 bromocriptine therapy. But of course, we're seeing  
6 also a contribution from the deterioration from  
7 baseline in the placebo group.

8 Well, we'd prefer not to see it -- a change  
9 in the placebo group -- but I must admit we've seen  
10 this quite commonly in recently reviewed NDAs. And it  
11 remains puzzling why we see it in tightly run studies  
12 but let's just say that it does happen.

13 Now, just a few comments about the effect of  
14 therapy on weight. It is a little disappointing that  
15 given the postulated mechanism of action across the  
16 studies, total body weight was essentially unchanged.

17 Now, there are some data that suggest that  
18 underlying this unchanged total body weight there may  
19 be a shift from adipose to lean body mass  
20 compartments.

21 However, even in the data that we have, I  
22 think that the magnitude of effect in terms of

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1 measured lean body mass, does not at all account for  
2 the fact that there was really -- well, in the study  
3 where there was a change in body weight, that does not  
4 account for the increase in body weight in study L, I  
5 believe.

6 I do think that it's, on the other hand,  
7 perhaps a positive aspect in that we have been  
8 concerned about the non-specific effect of anorexia  
9 caused by the drug and perhaps resulting in lowered  
10 food intake, and this could by itself, account for a  
11 benefit -- or could explain the results.

12 But it would seem that there is no major  
13 effect on weight and so at least we don't have to be  
14 too concerned about that possibility.

15 Now let's turn to durability of the efficacy  
16 as best we can, and go to the next slide, please.  
17 Now, you'll recall that all the patients in the  
18 placebo group are -- or at least are offered the  
19 chance to continue in an extension trial -- and they  
20 are titrated during the first part of the period  
21 following the end of the control trial.

22 Also, it's important to remember that the

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1 treated patients during the control part of the study,  
2 are actually discontinued from bromocriptine and  
3 retitrated.

4 This is the result in the adjunctive, the K  
5 and L trials. And you can see that there's actually  
6 a deterioration at first that you might expect, but  
7 then it does go back down. However, after week-60 it  
8 starts to go back up.

9 Of course, there continues to be patients  
10 dropping out from the extension trial so that our  
11 ability to infer very much with these small numbers is  
12 limited.

13 The next slide shows the results in the  
14 monotherapy extension studies, and you can see here  
15 it's a somewhat different pattern. They actually  
16 continue to fall after being discontinued from therapy  
17 and being retitrated, but maintain some degree of  
18 control -- or, the same level of control -- until once  
19 again, they start to go back up after week-52 or so.

20 Again, patient number is small -- you get  
21 small, progressively smaller, as you go out in time.

22 Now let's turn to safety issues in the next

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1 slide. And I will quickly mention the adverse events,  
2 or my estimate of the -- my review of adverse events.  
3 We'll key in on the cardiovascular events observed in  
4 the clinical trials, and we will give you the very  
5 little safety information, post-marketing experience  
6 that we have related to the cardiovascular problem.

7 Now this summary table just shows the  
8 percentage of patients with adverse events, and you  
9 can see that there is quite a difference between the  
10 treatment groups in favor of placebo as far as total  
11 adverse events.

12 There is also the same kind of proportion  
13 involved in the number of patients who discontinued  
14 the trial. Again, four patients on Ergo treatment  
15 were being -- ended up discontinuing. And that  
16 averages out to be about 12 or 13 percent.

17 We will quickly go through the frequent  
18 adverse events, starting with the most commonly  
19 observed problem which was nausea; 29 percent of the  
20 patients versus on the order of three to eight percent  
21 in the placebo groups has this particular problem.

22 Followed by asthenia, rhinitis, sinusitis,

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1 and the hypoglycemia issue has been discussed. And I  
2 really don't believe there is a problem there. We'll  
3 go on to the next slide which again will show us that  
4 there were eight MIs in all the clinical studies and  
5 eight were associated with Ergocet™ treatment, one  
6 was associated with placebo treatment.

7 Then all the other findings here I think  
8 really do not reach the threshold of concern. We can  
9 go on to the next slide and see that this particular  
10 series closed out. And then to the next slide let's  
11 look at -- let's talk about the cardiovascular events  
12 in the control trials.

13 In the pivotal studies themselves, K, L, and  
14 M, there were but four MIs and the bulk of them  
15 occurred in the treatment group of study K. There was  
16 one MI in the placebo group in study L, none in M.  
17 There were sporadic reports of angina pectoris, but  
18 there's certainly no imbalance there.

19 Well, if we simply look at the total number  
20 of cases that were reported for all studies combined,  
21 we find that there is a trend toward some kind of  
22 statistical significance in this particular imbalance.

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1           If we look just at studies K, L, and M,  
2 obviously, there is much less of one. There's really  
3 not much to be concerned about. Obviously, these --  
4 if we look at it this way, that is, the absolute  
5 number of events divided by numbers of patients, this  
6 is influenced by the fact that there were a number of  
7 patients in trials of fairly short duration.

8           The more appropriate way of course, as Dr.  
9 Testa has suggested, is to adjust for exposure, and  
10 we've done the same thing here. We haven't expressed  
11 the right in the same way, but the point is there is,  
12 after this adjustment, still a P value of .10 for the  
13 difference between treatment and placebo -- or  
14 myocardial infarction in all trials.

15           Now, I tend to agree with Dr. Testa that the  
16 problem is really driven by the fact that we had a  
17 very limited period of placebo observation, and we  
18 just happened to have only one case which probably is  
19 the aberrancy as opposed to the excess number in the  
20 treatment groups.

21           But this is still an issue that has to be  
22 thrashed out, and I hope that we can come back to that

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1 in our discussion.

2 Let us go on the post-marketing,  
3 cardiovascular reports. I won't go through the  
4 details here. Suffice it to say that there have been  
5 a number of domestic reports of bromocriptine  
6 associated cardiovascular events, but 80 percent of  
7 them, roughly, occur in women, mostly for the  
8 lactation suppression.

9 If you look at serious reports in men and  
10 women, men over age 60 and women over age 39 -- the  
11 period where the post-partum use would certainly have  
12 ended by -- you see that there are a very small  
13 number, absolute number, of cardiovascular reports in  
14 general. And we have not broken this down into the  
15 specific kinds of events. But this is from a fairly  
16 large post-marketing experience.

17 On the other hand we have to acknowledge,  
18 all of us, that cardiovascular reports are very  
19 unlikely to be typically reported in older patients --  
20 and that would be in this case, the Parkinson's  
21 patients who account for the large share now of  
22 bromocriptine use.

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1           So in summary, we can go to the final slide.  
2           I think we can all agree that Ergocet™ therapy has  
3           provided some efficacy in the control studies. The  
4           problem with nausea is prominent but it appears  
5           surmountable and can be minimized by careful  
6           escalation of the medication.

7           The safety profile of Ergocet™ appears  
8           generally acceptable, but again we need to discuss the  
9           higher rate of myocardial infarction associated with  
10          therapy.

11          And so with that, I conclude the FDA  
12          presentation. Thank you.

13          CHAIRMAN SHERWIN: Thank you. Are there any  
14          -- Dr. Davidson.

15          DR. DAVIDSON: Dr. Fleming, you know, in  
16          your post-marketing cardiovascular reports you  
17          mentioned that there were 137 out of 302 reports in  
18          women with serious events, and you said 15 out of the  
19          137 were ages higher than 39. Is that higher or lower  
20          than 39, because otherwise it means that most of the  
21          events occur in young females, less than 39. Did I  
22          understand correctly?

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1 DR. FLEMING: That's the point. That these  
2 are women who were using the drug for the indication  
3 of post-partum lactation, and there is another story  
4 about that particular use. We have not ever really  
5 fully resolved the issue, but there a number of  
6 reports of serious cardiovascular events in young  
7 women associated with bromocriptine therapy for  
8 suppressing lactation.

9 This was mentioned in the presentation by  
10 the company. This indication was withdrawn by Sandoz,  
11 the company that was marketing the drug for that  
12 indication, at the urging of FDA.

13 DR. DAVIDSON: Thank you.

14 CHAIRMAN SHERWIN: But they never resolved,  
15 you're saying, what was going on under those  
16 circumstances?

17 DR. FLEMING: Well, I don't think that it  
18 was ever really epidemiologically resolved in terms of  
19 there being some kind of ascertainment by -- it was  
20 not mechanistically resolved though there was a  
21 report, for example, of coronary spasm in a young  
22 woman undergoing an angiographic procedure, who was on

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1 the drug at the time.

2 So it, unfortunately, is a situation where  
3 we, in a particular application of this therapy had a  
4 number of reports that I believe the gestalt would be  
5 of some concern and certainly the risk benefit  
6 relationship was considered unacceptable. It was not  
7 that we had a firm picture of the causal relationship.

8 And perhaps Dr. Sobel or Dr. Bilstadt might  
9 want to comment further about that.

10 DR. SOBEL: Yes. We never resolved it  
11 fully. We did have -- actually with post-partum  
12 lactation our chief concerns were in regard to stroke  
13 and convulsions, and various analyses of that was not  
14 definitive. We did ask for a prospective study -- not  
15 a prospective study, a case control study -- which  
16 yielded some information but not very good  
17 information.

18 We eliminated a risk of greater than five  
19 for stroke. That study was not large enough to  
20 eliminate smaller degrees of risk, so the drug was  
21 withdrawn. But the issue was never completely  
22 resolved.

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1 DR. MOLITCH: I think there were subsequent  
2 case control studies of fairly large numbers of women  
3 that never did substantiate those findings.

4 DR. FLEMING: That's correct.

5 CHAIRMAN SHERWIN: Thank you very much, and  
6 we're only ten minutes behind time which means that we  
7 can begin -- have lunch, which is amazing so early in  
8 the day -- and I think we can begin in an hour from  
9 now, which would be promptly at ten-after-one.

10 (Whereupon, a brief luncheon recess was  
11 taken at 12:10 p.m.)

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

2 1:17 p.m.

3 CHAIRMAN SHERWIN: We're beginning to  
4 introduce the afternoon session which is an open  
5 discussion by the committee regarding issues related  
6 to the presentation. And I'm told that Dr. -- I know  
7 that Dr. DeFronzo has to give a talk tonight and so I  
8 would ask, to expedite things, if we could focus on  
9 his presentation right now in the beginning, and then  
10 I understand that Dr. Steiner also has a commitment.

11 And so the lipid issues I think we should  
12 focus on then. And then from then on we can do it any  
13 way we would like.

14 So I'd like to hear if anybody on the  
15 committee has any questions for Dr. Defronzo.

16 DR. HIRSCH: I understood the data on the  
17 density -- were those actually done by underwater  
18 weighing with your patients or not? Who got the  
19 density measure and who didn't?

20 DR. DeFRONZO: In the clamp studies we did  
21 underwater weighing -- and that's the way all the data  
22 are expressed -- tritiated water and impedance

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1 densitometry. And there were no changes, as I said.  
2 They give basically the same results.

3 Now, Anthony can comment on the clinical  
4 studies, but in one of the clinical studies underwater  
5 weighing was also carried out. Is that correct,  
6 Anthony?

7 DR. HIRSCH: Oh, the reason I ask is  
8 obviously -- it's a very important point as to whether  
9 there was any weight change, because weight change  
10 along can produce some of the things you were saying,  
11 apart from any drug effect.

12 And the reason weight change does it is  
13 because it changes the fat mass. So a change in fat  
14 mass then, is an equal explanation for why free fatty  
15 acid turnover changes, or triglycerides -- etc., etc.  
16 So I'm sort of seeing how to figure this one out.

17 DR. DeFRONZO: All I can tell you is that we  
18 have three independent measures of fatness, and  
19 there's absolutely no change using the three  
20 independent measures. We have body weight -- there  
21 was absolutely no change. So in our study --

22 DR. HIRSCH: I mean, the guy is carrying

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1 lead in his pocket. I mean, how does the density  
2 change? I don't understand --

3 CHAIRMAN SHERWIN: Well, your measurements  
4 I don't think, looked at density, right Ralph? Dr.  
5 Cincotta can discuss that --

6 DR. HIRSCH: Well, someone just help me with  
7 what the compartmental changes are thought to be.  
8 Either there was a fat change -- if the density went  
9 up that means less fat.

10 DR. DeFRONZO: There are two different  
11 issues, okay? In our studies no measurement of fat-  
12 free mass body weight, intra-abdominal fat or  
13 subcutaneous fat changed, whatsoever. So if there are  
14 no changes then one cannot explain the improvement in  
15 insulin sensitivity that we observed, on the basis of  
16 any change in body fat or composition as measured by  
17 the NMR.

18 DR. HIRSCH: So the density did not rise in  
19 your studies?

20 DR. DeFRONZO: That is correct.

21 CHAIRMAN SHERWIN: But you didn't -- Dr.  
22 Cincotta, I think you ought to comment because my

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1 understanding is that you studied many more patients  
2 --

3 DR. CINCOTTA: Right.

4 CHAIRMAN SHERWIN: And so the power of your  
5 analyses would be stronger -- even through it's more  
6 limited in its scope, is that correct?

7 DR. CINCOTTA: That's correct. In the study  
8 K we did measure body density again, using the same  
9 technique, underwater weighing. What we found was  
10 that for the Ergocet™ group, relative to their  
11 baseline, there was an increase in the body density.

12 However, for the placebo group there was  
13 not. That between-group differences, although showed  
14 a trend towards increased body density, did not reach  
15 statistical significance.

16 And remember again, these were individuals  
17 that were rigorously weight-maintained throughout the  
18 course of the study as you can see by the body weight  
19 data that I showed earlier. There was no major  
20 changes in body weight.

21 DR. HIRSCH: Well, that's the point. I  
22 mean, obviously one wants to look at error measures

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1 and all sorts of things, but given those as facts,  
2 then clearly the Ergocet™ group had less fat. That's  
3 the only way you can increase density and maintain  
4 constant body weight. There's no other way of doing  
5 it.

6 DR. DeFRONZO: Right, increase the lean to  
7 fat administration --

8 DR. HIRSCH: You're saying that the  
9 Ergocet™-treated people had a reduction in body fat?

10 DR. DeFRONZO: Well, we measured the  
11 density. The density is the absolute measure. to  
12 then translate that into body fat there are several  
13 assumptions that go into those equations. But the  
14 absolute calculation that can be derived without any  
15 assumptions or without any calculation, is the density  
16 -- the underwater weight.

17 That did go up and suggests that the lean to  
18 fat mass ratio relative to the baseline, increased.  
19 Now, you know, a small increase in the body weights  
20 over time didn't change. I should point out that  
21 increase in body density without changing body weight  
22 is not an uncommon phenomenon when one looks in the

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1 wild at the animals going through their annual cycle.

2 DR. HIRSCH: Let me pursue that just one  
3 moment. I mean, one way to do that is to increase  
4 physical activity and increase -- were there any  
5 measures of physical activity in the two groups?

6 DR. CINCOTTA: No, there were essentially no  
7 behavioral analyses done on individuals over the  
8 course of the 24-week treatment period.

9 DR. HIRSCH: But just to complete this thing  
10 from my own point of view, it looks very reasonable  
11 that if these data are correct that the amount of body  
12 fat declined, and the fact that the body fat declined  
13 could be a major explanation for many of the  
14 parameters you're saying and instances -- and without  
15 having to implicate in a ventromedial nucleus or other  
16 kind of more -- other theories.

17 DR. CINCOTTA: Well, first of all, going  
18 back to the ventromedial hypothalamus, if you recall,  
19 infusion of norepinephrine and serotonin into the VMH  
20 actually caused an increase in body fat mass in our  
21 animal studies. And it was actually quite  
22 substantial.

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1           So it can't explain the obesity, in and of  
2           itself, number one. Number two, in our clinical  
3           trials -- again, in Dr. Defronzo's studies and in our  
4           studies -- in neither case do we see statistically  
5           significant change relative to the placebo, in either  
6           the body weight or the body density, relative to the  
7           placebo.

8           CHAIRMAN SHERWIN: Just before Dr. Marcus,  
9           are there any other questions for Dr. DeFronzo? I'm  
10          told he has a 2 o'clock flight and he'll never make it  
11          unless he gets out. In fact, I'll never make it, so  
12          I think you'd better go, Ralph.

13          Assuming there's no burning questions, so we  
14          can go on. Dr. Marcus.

15          DR. MARCUS: In a corollary to Dr. Hirsch's  
16          question about body composition, is there any reason  
17          to believe that this agent may directly cause  
18          retention of salt and water; that the changing  
19          relationship of adipose mass to lean body mass, or  
20          non-adipose mass, could in fact be accounted in part  
21          by increased water compartment?

22          I don't think your bioelectric impedance

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1 measures could distinguish between a change in real  
2 muscle mass from water. I wonder about any of the  
3 other measurements.

4 DR. CINCOTTA: That's an intriguing point  
5 and my only comment on it, as it relates to the water  
6 compartment is that if in fact we're seeing an  
7 increase in body density and it can be ascribed to an  
8 increase in protein mass or an increase in the protein  
9 to fat mass, then if the protein actually is  
10 increasing then the water hydrated to the protein is  
11 going to increase.

12 Again, we don't have those data in humans,  
13 but when one looks at animal studies, you do tend to  
14 see, not only a reduction of the body fat in the  
15 animals treated with bromocriptine, but an increase in  
16 the total protein in the animals. And we've seen this  
17 -- and other laboratories have seen it and published  
18 it in several species. So that might be occurring as  
19 it relates to the protein mass.

20 DR. MARCUS: May I continue with some  
21 questions?

22 CHAIRMAN SHERWIN: You may continue.

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1 DR. MARCUS: Thank you. As someone who has  
2 been exposed to Gerry Reaven on an almost daily basis  
3 for 20 years, I'm delighted to see that people are  
4 paying attention to triglycerides and other important  
5 heart and vascular disease risk factors in diabetes.

6 I'd like to explore a few of those issues.  
7 For example, you did talk about in your narrative, in  
8 the briefing book, you did talk about measurements of  
9 HDL, LDL, PAI-1 -- and although you didn't mention it,  
10 fibrinogen would be another cardiovascular risk  
11 factor.

12 But you haven't shown us any data on how  
13 those change, and in fact your lipoprotein data were  
14 based on indirect measures of LDL; that is, you used  
15 the indirect beta quant in people whose triglycerides  
16 were 700, which are not valid methods.

17 So I wonder what you can now take your time  
18 and tell us what happened to all these coronary heart  
19 disease risk factors.

20 DR. CINCOTTA: You're exactly right about  
21 the association of those lipoprotein moieties and PAI-  
22 1 with hypertriglyceridemia. We did point that out

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1 earlier.

2 And actually, as you bring up Gerry Reaven's  
3 study, I just want to mention -- to answer your  
4 question in part -- we did study with Gerry Reaven in  
5 obese, non-diabetic subjects, and the results of that  
6 trial -- it was an essentially 8-week study. We  
7 published it in Diabetes Care approximately a year  
8 ago.

9 And what we found was, just as in the  
10 diabetic population we did see, over the course of the  
11 24 hours of the day in his study at Stanford with Ida  
12 Chen, a reduction in both the triglycerides and the  
13 free fatty acids over the day. So it's similar.

14 In his study where he analyzed the different  
15 subjects -- they were actually isolated -- again he  
16 saw essentially the same results that we have showed  
17 here today: a reduction in the total cholesterol, no  
18 change in the HDL cholesterol, although there was a  
19 trend towards an increase and a trend towards a  
20 decrease in the LDL cholesterol in his study, was the  
21 n number was much smaller -- I think we had 15  
22 patients -- and the ratio of HDL to LDL in that study,

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1 did increase. The P value was .06, I believe. If you  
2 looked that paper up it's in there.

3 Getting to our Phase 3 data, unfortunately  
4 we did not measure PAI-1 or any fibrinogen factors,  
5 and as you mentioned, our analysis for LDL was not  
6 from a determination and isolation, but rather from a  
7 calculation. So the only value we have that was  
8 actually determined was the HDL cholesterol, and it  
9 was unchanged in this group.

10 What did change was the total cholesterol,  
11 similarly as Gerry Reaven published, in this patient  
12 population. And given the fact that LDL and HDL  
13 aren't changing, there's a likelihood that it  
14 represents the VLDL cholesterol moiety which would fit  
15 with lowering the triglycerides.

16 I don't know, maybe Dr. Steiner may want to  
17 talk to that point more. But to answer your question,  
18 unfortunately we didn't measure PAI-1 or fibrinogen  
19 factors in this Phase 3 study. It would be of extreme  
20 interest to do so and actually we have a study we have  
21 planned to do so --

22 DR. MARCUS: I think you're right. I think

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1 that the bias was introduced by using the indirect  
2 beta quant method it would artificially raise the LDL  
3 so that in truth, your conclusion that it's mostly  
4 VLDL is probably -- Roger is in agreement? Okay.

5 Why did you exclude people who were taking  
6 metformin, in your studies?

7 DR. CINCOTTA: Oh, that's an easy one, thank  
8 God. During the course of the study, metformin was  
9 not an FDA-approved drug at that point in time.  
10 Therefore, we excluded individuals that may have been  
11 using it as an experimental drug. And that was an  
12 experimental drug exclusion.

13 DR. MARCUS: Now, if this drug were approved  
14 for use in association with oral hypoglycemic agents,  
15 and it were out on the open market, then presumably  
16 there would in fact, be a lot of Type 2 diabetics who  
17 are currently taking insulin but under poor control,  
18 who might be tempted -- the physicians might be  
19 tempted to place them on this drug as well.

20 And the question that I would have is, do  
21 you have any knowledge or reason to have knowledge,  
22 about what this agent would do to the recovery from

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1 hypoglycemia that might have been induced by insulin?

2 That is, could there be -- I understand --

3 DR. CINCOTTA: Okay, right.

4 DR. MARCUS: -- there was no direct  
5 hypoglycemic threat --

6 DR. CINCOTTA: Right.

7 DR. MARCUS: -- from bromocriptine itself,  
8 but interacting with insulin, is that a theoretical  
9 issue?

10 DR. CINCOTTA: Right. Okay. I can address  
11 that issue like this. We do have some information,  
12 and I'm actually glad that you asked. Which that  
13 information that we've made available, I don't  
14 believe, publicly even, yet, to anyone, and it's  
15 nothing that we've presented to the FDA for the panel  
16 to review.

17 However, we did just finish a study where we  
18 employed Ergocet™ as an anti-diabetic agent in  
19 patients on insulin. And if I recall the treatment  
20 design -- study design, rather -- they were on 4.8  
21 milligrams Ergocet™ per day, they were treated for  
22 approximately 16 to 20 weeks -- I believe 16 weeks --

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1 actually, it's 12 to 16 weeks, I'm sorry.

2           And at the end of treatment, what we saw was  
3 HbA1c declining by 0.7 in the Ergocet<sup>TM</sup>-treated group,  
4 and an increase of 0.5 in the placebo group on insulin  
5 -- everyone on insulin all the while.

6           I'm sharing with you data that we haven't  
7 even fully analyzed ourselves, but you can see from  
8 those numbers that in fact the effect in the insulin-  
9 treated population is very similar to what you see in  
10 adjunctive therapy and is very similar to what we see  
11 as monotherapy.

12           And that fits well with its mechanism of  
13 action. And as far as hypoglycemic events in that  
14 study -- are you aware of the data on hypoglycemia --  
15 okay. I'm going to turn it over to Rich Paul to  
16 comment on hypoglycemic events in the insulin sparing  
17 study.

18           DR. PAUL: The data of course, is not  
19 completely analyzed yet, but I can tell you, is I look  
20 at each and every adverse event that comes rolling  
21 through. We have not had any, i.e., serious  
22 hypoglycemia whatsoever.

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1           CHAIRMAN SHERWIN: Regarding that issue, I  
2 don't have full data either, but I do think it would  
3 be important to look at that because there is that  
4 potential that by altering neurotransmitters in the  
5 VMH that you may influence central awareness and alter  
6 catecholamine responses to hypoglycemia.

7           I mean, the data that you have and based on  
8 the hypothesis, would be that you would decrease  
9 sympathetic discharge as well as counter-regulatory  
10 hormones, and that there is data suggesting that  
11 norepinephrine within the VMH is a triggering signal  
12 for counter-regulatory responses.

13           So theoretically, blocking that might  
14 actually impair recovery from hypoglycemia, and surely  
15 that's something that should be look at before any  
16 recommendation could be made about insulin and the  
17 drug.

18           DR. CINCOTTA: Yes, that's a very good  
19 point. And to that point I'd like to mention the  
20 available evidence that we have to analyze that  
21 situation.

22           In the diabetic animal models that we've

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1 studied, we see relative to the non-diabetic animal  
2 models, elevated levels of norepinephrine and  
3 serotonin in the VMH. And classically an increase in  
4 the glucagon levels peripherally, and insulin  
5 resistance, lipolysis, high free fatty acid levels as  
6 I described earlier this morning.

7 Following treatment with the dopamine  
8 agonist we tend to see the reduction of those elevated  
9 levels of norepinephrine and serotonin that come down  
10 to the normal level, not to any subnormal level.

11 CHAIRMAN SHERWIN: Right. But during  
12 hypoglycemia you trigger the release of norepinephrine  
13 perhaps --

14 DR. CINCOTTA: Right.

15 CHAIRMAN SHERWIN: -- and so you might under  
16 those circumstances, diminish that acute release in  
17 the VMH. It's possible, that's all I'm saying.

18 DR. CINCOTTA: Yes.

19 DR. MOLITCH: Along those same lines, you  
20 can't really extrapolate data from the rat to the  
21 human with regard to counter-regulatory hormone  
22 response to hypoglycemia. As you well know, growth

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1 hormone is suppressed in the rat with hypoglycemia and  
2 it's stimulated in the human.

3 So I think that you just cannot at all,  
4 extrapolate this data. And I think we really clearly  
5 need human studies to look at counter-regulatory  
6 hormone response for hypoglycemia.

7 DR. CINCOTTA: Yes, I wasn't inferring that  
8 I was trying to extrapolate. I agree with you 100  
9 percent. I was just merely stating what we actually  
10 do see in the diabetic versus the non-diabetic animal  
11 --

12 DR. MOLITCH: Are there anything in the  
13 data?

14 DR. CINCOTTA: No, we don't have at this  
15 point in time, any human data on VMH levels of any  
16 catecholamines --

17 DR. MOLITCH: No, no, no --

18 DR. CINCOTTA: The kind of regulatory  
19 responses?

20 DR. MOLITCH: Regulatory responses.

21 DR. CINCOTTA: No. At the present time we  
22 do not. Anything with bromocriptine treatment,

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1 getting back to Gerry Reaven's study, the one piece of  
2 information that we do have that comes -- that  
3 approaches coming close to it -- doesn't relate to  
4 catecholamines. It's rather the growth hormone.

5 And the levels of growth hormone that you  
6 normally see in obese individuals are dramatically  
7 reduced compared to the lean population. And  
8 especially so during the evening hours when growth  
9 hormone normally peaks.

10 In the study we did with Gerry Reaven,  
11 following eight weeks of treatment those very low  
12 levels of growth hormone actually began returning to  
13 the control levels that you see in a lean population;  
14 the before and after difference was statistically  
15 significant. And it was mostly due to the return of  
16 the nocturnal peak of growth hormone following the  
17 drug treatment.

18 DR. KATZNELSON: You know, on that line  
19 about growth hormone, I meant to ask you about this.  
20 There's old data in pediatric populations and adults  
21 that if you give dopamine agonists they'll result in  
22 increase in growth hormone secretion, and probably

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1 even elevations in IgF-1 levels. Usually within  
2 normal range; sometimes even beyond that I've seen  
3 clinically.

4 And of course, this can affect glucose  
5 homeostasis. It may have something to do with some of  
6 your lean mass measurements, too, that you discussed.

7 DR. CINCOTTA: Right.

8 DR. KATZNELSON: Do you have any data  
9 further on mean growth hormone levels or IgF-1 levels  
10 as a surrogate marker?

11 DR. CINCOTTA: Yes, yes we do. And again,  
12 I'm going to have to refer you to studies that were  
13 done in the obese insulin-resistant, non-diabetic  
14 population.

15 And when we did measure growth hormone and  
16 IgF-1 simultaneously, what we found was that although  
17 the growth hormone levels that were very low in that  
18 patient population, they tended to return to normal --  
19 to the normal level. They didn't quite reach normal,  
20 but they tend to return towards normal, during the  
21 nocturnal portion of the day.

22 When we measured IgF-1 over the entire

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1 course of the day in those same subjects, we didn't  
2 see any change.

3 DR. KATZNELSON: Well, it's unlikely you'll  
4 see much of a change in IgF-1 over the day, but how  
5 about over the weeks? What did you see?

6 DR. CINCOTTA: It was relative to their  
7 baseline. So over a 2-month period of treatment we  
8 didn't see any change.

9 CHAIRMAN SHERWIN: Maria.

10 DR. NEW: I have just brief, short  
11 questions. First, are you surprised that with the  
12 fall in glucose levels which you've shown, that your  
13 hemoglobin A1c did not show a greater fall than you  
14 have?

15 DR. CINCOTTA: The drop in the glucose  
16 levels in the fasting and post-prandial states when we  
17 measured them diurnally, was in the monotherapy and  
18 adjunctive therapy studies, approximately 30 to 40  
19 milligrams and 30 to 35 milligrams, respectively, the  
20 A1c relative to the control.

21 And the A1c delta relative to the controls  
22 about 0.5 -- .5/.6 -- which are fairly I think, a

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1 fairly good approximation of each other. Actually, if  
2 you looked at Ralph DeFronzo's data earlier this  
3 morning, his were in the similar range.

4 His A1c delta was a little larger than ours.  
5 It was at 16 weeks but it was at 1.1 delta relative to  
6 the placebo. And his glucose delta was also a little  
7 bit larger than ours but proportionally right on with  
8 our data. Whereas our was like 30 to 40, his was  
9 almost 55 -- it was, almost 55 milligrams per  
10 deciliter delta relative to placebo.

11 DR. NEW: Then I'd like to ask this to the  
12 clinicians in your group. I understand biostatistical  
13 significance was shown in the fall of the hemoglobin  
14 A1c when you measured the delta at .55 overall. But  
15 for the clinician, would a change -- well, first let  
16 me tell you.

17 The Ergocet™ group overall, the hemoglobin  
18 A1c was 9.23, and that of the placebo was 9.85 for  
19 study K. For study L it was 8.93 Ergocet™ versus  
20 placebo, 9.66, and for M, 8.99 versus placebo, 9.09.

21 Now, I don't take care of Type 2 diabetics  
22 very often because I'm a pediatrician but to me, if I

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1 saw these changes in hemoglobin A1c, I would not  
2 consider them clinically significant. And so I'm  
3 asking you about that, and perhaps you can tell me  
4 what other drugs have produced in the way of a fall of  
5 the hemoglobin A1c that are currently in practice in  
6 Type 2 diabetics.

7 DR. PAUL: That's a very good question, and  
8 I believe I have a good answer for you. As a  
9 clinician I can speak not only to having worked in the  
10 arena of -- industry, but I spent over a decade  
11 treating primarily Type 1 and Type 2 people with  
12 diabetes. And so I fully understand where you're  
13 coming from.

14 What I tend to look at when I view patients  
15 -- or I reviewed patients was, I wanted to make sure  
16 that I understood what benefit I was giving that  
17 patient by whatever treatment that I was prescribing.  
18 And I think what has to be understood here is the  
19 magnitude of benefit that a patient would indeed  
20 derive from these falls in hemoglobin A1c.

21 I'd like Dr. John Lachin to address this  
22 magnitude of fall for us in respect to what the

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1 benefit would be. Dr. Lachin.

2 DR. LACHIN: I can't address the clinical  
3 interpretation or the clinical implications of this in  
4 terms of the pattern that we saw in those curves. It  
5 would have been nice had the placebo group stayed at  
6 a constant level of about nine and the, you know,  
7 treated group had a consistent fall that stayed, you  
8 know, at about eight-and-a-half or less.

9 But we saw an increase in both groups. And  
10 that could be due to any number of things. It could  
11 be due to cohort effects of some kind; it could be due  
12 to changes in the way the patients adhere to their  
13 treatments over time. So that makes this question a  
14 little more difficult to address.

15 In the original DCCT we randomized patients  
16 to intensive versus conventional treatment, and there  
17 were slight changes in the A1c over time in both  
18 groups, but pretty much we knew that the A1c was  
19 reduced substantially in the intensive group, and it  
20 was maintained at a level of about nine in the  
21 conventional group. So it made the interpretation of  
22 that a little easier.

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1           Now, what I'm going to try and do is  
2 translate the treatment group differences that were  
3 observed in the DCCT to the interpretation of the  
4 figures that were presented this morning.

5           And let me just briefly show you the data  
6 from the DCCT that this is based on. Some of the  
7 members of the committee saw me present this at the  
8 last meeting. I'm just going to show you two slides.

9           Basically what happens is, when we look at  
10 the log of the mean A1c during the study and compare  
11 that to the log of the risk of developing progression  
12 of retinopathy, we see this straight, linear  
13 relationship.

14           Which means that there is a constant of  
15 proportionality when we look at this in terms of the  
16 mean HbA1c versus the actual risk. We go from a  
17 linear relationship between the log of A1c versus the  
18 log of risk, to a non-linear relationship between the  
19 mean of A1c and the expected risk.

20           Now, what we have done is now taken the  
21 figures from this curve -- I show you the curve here  
22 for the intensive treatment group. In fact, we did

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1 the computations using the conventional treatment  
2 group because in the DCCT the mean A1c in the  
3 conventional treatment group was about nine, which is  
4 more comparable to what we've observed among these  
5 patients.

6 And of course, this is translating a  
7 finding, an IDDM to NIDDM, and of course there are a  
8 lot of questions about whether or not that's  
9 reasonable, but I think it's the best data we have to  
10 go on that would allow us to relate the relationship  
11 between the HbA1c levels achieved, the changes in the  
12 HbA1c levels, and the changes in risk.

13 Now with that, let me --

14 DR. NEW: Perhaps I could just simplify my  
15 question by asking you, on Type 2 diabetes if instead  
16 of giving bromocriptine you would be giving -- I don't  
17 know, sulfonylurea. What kind of a drop from the  
18 hemoglobin A1c would you expect?

19 DR. LACHIN: I'm not the person to address  
20 that.

21 DR. DAVIDSON: Well, you know, the average  
22 lowering of A1c with sulfonylureas is about one-and-a-

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1 half percent.

2 DR. SOBEL: As a monotherapy.

3 DR. DAVIDSON: As monotherapy.

4 DR. SOBEL: One of our medical officers  
5 anticipated the question and made up a chart of what  
6 we saw with our last four approvals. And this without  
7 adjusting for placebo. I think this is what you  
8 wanted to know.

9 DR. NEW: Yes, that's exactly what I wanted  
10 to know.

11 DR. SOBEL: That's what I thought. Well,  
12 for repaglinide it was -1.9 -- I'm just giving the  
13 unadjusted; troglitazone, -1; metformin, -1.4; and  
14 acarbose, -0.7.

15 Now, with the placebo adjusted, as was done  
16 with Ergocet™, the difference is as follows:  
17 repaglinide, -2.8; troglutizone, -1.4; metformin, -  
18 1.8; and acarbose, -0.76.

19 DR. MARCUS: Excuse me Sol, was that -- were  
20 those the intention-to-treat data or were --

21 DR. SOBEL: Yes --

22 DR. MARCUS: -- those the response --

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1 intention to treat?

2 DR. SOBEL: Those are intention-to-treat  
3 data. Let me just make one other point while I'm  
4 talking. In looking at -- and Dr. Zan Fleming alluded  
5 to it briefly in his presentation -- in looking at --  
6 well, let's look at the predominance source of data  
7 which was K and L.

8 If one looks at the baseline data -- Zan  
9 mentioned there was a trend but it was a fairly  
10 powerful trend -- on page 48 of the Ergocet™ handout.  
11 The bottom of the page, disease duration; Ergocet™  
12 group it was 5.8, where the control group was 6.7, and  
13 that got pretty close to significance at 0.06.

14 And turning the page, the fasting glucose in  
15 the control group at the beginning, was 226; in the  
16 Ergocet™ group it was 218 with the P value .08. The  
17 reason I'm mentioning this is that most of the  
18 efficacy being discussed here rests on the difference  
19 between the drug and placebo. The biggest  
20 contribution is the placebo worsening.

21 Now, if the placebo group was apparently  
22 further along in the disease process, one would expect

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1 that the underlying worsening would be more for the  
2 placebo. I just mention this because of the relative  
3 --

4 DR. SIMPSON: Can I just -- it's related to  
5 this. I don't know where I saw it, but one of the  
6 comments made was that a clinical significant  
7 difference would be a drop in one percent. And yet I  
8 haven't seen any data showing how many people actually  
9 dropped one percent -- from baseline.

10 DR. NEW: If I could just clarify your  
11 question.

12 DR. SIMPSON: Okay.

13 DR. NEW: I understand that the minus-1  
14 percent has to be the difference between the placebo  
15 and the treated, not just the baseline treated to the  
16 end of the treatment. It's the difference between  
17 placebo and the treated, and that's more than one  
18 percent.

19 DR. SIMPSON: Okay. Whatever.

20 DR. NEW: Am I right? Dr. Fleming, am I  
21 right or am I wrong?

22 DR. CINCOTTA: Well, let's look at the slide

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1 here. I think this may help clarify --

2 DR. NEW: The treatment effect is the  
3 difference between the placebo and the treatment and  
4 they've demonstrated a greater than one percent change  
5 --

6 DR. SIMPSON: No, they haven't. They  
7 haven't given us any figures on that.

8 DR. SOBEL: I was going to read you  
9 something off the sheet. Okay, I'll read them. For  
10 Table 9 the drug effects for -- this is the  
11 monotherapy chart.

12 DR. CINCOTTA: The data up on the screen may  
13 show what we're looking for here. First of all, the  
14 .56 delta relative to the placebo group that's  
15 observed as early as 12 weeks of treatment, is  
16 maintained out to 24 weeks of treatment. And it  
17 represents the mean of the entire population treated  
18 with Ergocet™ versus the mean of the entire  
19 population treated with a placebo.

20 And subjects exposed to the exact same  
21 experimental conditions. If you want to look at on a  
22 per patient basis in the way medicine is practiced on

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1 an individual basis, and try and get at some of the  
2 questions that you're I think, alluding to, one can  
3 take the datasets of all the subjects treated with  
4 Ergocet™, categorize them as we've done here -- delta  
5 from the baseline, from the beginning to the end of  
6 the study -- and you can see that for individuals --  
7 this is an adjunctive therapy study -- 60 percent of  
8 all the subjects treated have a minimum of .3 or  
9 better drop from the baseline.

10 As you go out, a 0.7 drop from the baseline  
11 represents 40 percent of all the subjects in the  
12 study, and your question of reaching the 1.0 percent  
13 -- it's 30 percent of all subjects treated receive a  
14 1.0 drop from the baseline.

15 Getting to the point of --

16 DR. SIMPSON: How many in the placebo also  
17 achieve that?

18 DR. CINCOTTA: In the placebo groups -- we  
19 have the slide -- it's roughly, at least a half or  
20 one-quarter the further that you go out. I believe we  
21 have that slide somewhere. Let me check in our  
22 backups.

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1 DR. DAVIDSON: And how about study K? Do  
2 you have study K on that?

3 DR. CINCOTTA: Yes. We have all -- I  
4 believe all three studies -- the same trend, the same  
5 --

6 CHAIRMAN SHERWIN: We would like to see the  
7 -- this would be important so we would need the  
8 control data and study K. And study M as well.

9 DR. NEW: May I just clarify my question  
10 again? I'm sorry to --

11 DR. CINCOTTA: So here are the data from  
12 study K relative to the placebo. The percentage of  
13 all subjects receiving or obtaining a .3, .5, .7, etc.  
14 -- a minimum of .3, a minimum of .5 -- drop from the  
15 baseline over the 24-week treatment period relative to  
16 the placebo.

17 You can see roughly from .5 on it's double  
18 or triple the number of the placebo subjects and the  
19 statistical analysis shows it's significant at all of  
20 those categorical cutoff points.

21 So if you want to see the same situation for  
22 study L -- here's study L and you can see again,

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1 essentially the same trend. It's at least double, in  
2 many cases triple -- especially the further out you  
3 go, the 1.0 percent. It's four times higher than what  
4 is seen for the placebo group.

5 Again, all statistically significant; there  
6 really is a study drug effect going on here which  
7 could be, you know, observed with the entire intent-  
8 to-treat population without categorizing it. But this  
9 is how it breaks out when you do categorize it.

10 And then again for study M, you see a  
11 similar situation over the cutoff points. So again,  
12 getting at the reproducibility of the response to the  
13 drug relative to the placebo group.

14 DR. NEW: These are completers?

15 DR. CINCOTTA: This is over the 24-week  
16 treatment period. These individuals that completed  
17 therapy over the 24 weeks. There is no real  
18 difference if you'd look at completers or the LOCF,  
19 which is similar to our HbA1c for the entire  
20 population.

21 DR. DAVIDSON: Why do you think there's a  
22 big difference in the -- at least the .3 percent. You

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1 know, in this group it's roughly 43 percent, in study  
2 L was 60 percent --

3 DR. CINCOTTA: Go back to study L.

4 DR. DAVIDSON: There's a big -- significant  
5 difference in the two. How could you explain the  
6 difference in these two studies with the numbers?

7 DR. CINCOTTA: Well, the -- if you look at  
8 studies K, L, M side-by-side, there's not a gigantic  
9 difference between them. The trends are nearly  
10 exactly the same. There is a greater percentage of  
11 patients in this particular study that are getting an  
12 improved response.

13 This happens to be an adjunctive therapy  
14 study. If we look at study K again, it's similar to  
15 what you see in study M, but the trends are the same  
16 for K, L, and M. Do we have a slide of K, L, and M  
17 combined? Let's look if we take all the data and you  
18 look at all three studies, the slide doesn't -- you  
19 know, it's the same picture over and over and over  
20 again.

21 CHAIRMAN SHERWIN: Did you finish, Dr.  
22 Simpson? Dr. Molitch.

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1 DR. MOLITCH: My understanding is from, I  
2 guess the questions I've asked before is, that you do  
3 not have prolactin data to go along with this for  
4 correlations, or you do? The degree of prolactin  
5 suppression -- does that correlate with --

6 DR. CINCOTTA: Let me -- yes, we --

7 DR. MOLITCH: -- what's the improvement?

8 DR. CINCOTTA: We have the data. Let me  
9 just say a couple of things about the prolactins so  
10 that we get on the same sort of page here with  
11 prolactin.

12 All of our available data from our animal  
13 studies indicate a central mechanism of action. When  
14 we move to our human studies we didn't have the luxury  
15 of analyzing central changes responding to the drug.

16 Prolactin was used only as a surrogate  
17 marker to find only the threshold dose -- the 1.6  
18 milligram dose. Beyond that it has no real relevance  
19 to anything that we're looking at here. And I do  
20 actually -- we got the data during lunch I can show  
21 you.

22 When you raise the Ergocet<sup>TM</sup> dosage up to

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1 4.8 milligrams as you would well imagine, these are  
2 not hyperprolactinemic subjects by definition. And  
3 they're all essentially reduced to well within the  
4 normal range, regardless of response to the -- I'm  
5 sorry, regardless of the glycemc response to the  
6 drug.

7 DR. MOLITCH: I'd actually like to see the  
8 levels that they're reduced to --

9 DR. CINCOTTA: Okay.

10 DR. MOLITCH: -- because this to me, has  
11 major importance in the adverse effects that you have  
12 not talked about. And that is, in taking a normal  
13 prolactin and lowering it to unusually low levels.  
14 And does that have any clinical effects?

15 We know that there are prolactin receptors  
16 on a variety of tissues in the body including  
17 reproductive tissues, and it's important for  
18 spermatogenesis. And so that reducing all prolactin  
19 levels to low levels may actually have some importance  
20 that I have not heard addressed yet.

21 DR. CINCOTTA: Right. And that's a good  
22 question, actually, and let me gather the numbers and

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1 we'll take a look at them.

2 DR. PAUL: I thought it would be helpful to  
3 share with you before we leave this issue, some actual  
4 numbers and percentages when one compares Ergocet™ to  
5 placebo, and a statistical comparison done between  
6 those groups.

7 In the completer population, 34 percent  
8 versus 15 percent achieved the one percent. In the  
9 final -- 24-week final point -- 35 percent for K and  
10 L combined, versus 16 percent. Both of those were  
11 highly, statistically significant out to at least  
12 three decimal places -- .0027 and .0013 respectively.

13 When you look at study M for the same  
14 percentages of those patients who achieve that one  
15 percent, 28 percent versus eight percent for placebos;  
16 24 percent in the final endpoint versus eight percent  
17 for placebo. Again, highly statistically significant.

18 CHAIRMAN SHERWIN: Dr. New and then Dr.  
19 Hirsch.

20 DR. NEW: Dr. Fleming, I'm trying to get  
21 clarified -- in the handout which you gave and you all  
22 presented, it says the primary objective is to

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1 demonstrate a clinically significant difference which  
2 is defined as a reduction of one percent or greater in  
3 the level of glycated hemoglobin in subjects treated  
4 with bromocriptine plus an ADA diet when compared to  
5 a placebo control group.

6 So in other words, at least this study  
7 objective as printed says that the difference between  
8 the placebo and the treatment group has to be greater  
9 than one percent. It doesn't say in this objective  
10 that the treatment group from baseline to endpoint has  
11 to be greater than one percent.

12 I'm just trying to clarify, what is the  
13 rule?

14 DR. FLEMING: Yes, this is obviously, a  
15 protocol definition. And I'm trying to understand  
16 your question, Dr. New. I'm sorry.

17 DR. NEW: At the end of the 24-week -- let's  
18 take the 16 weeks where they have the most data. If  
19 you take the placebo level of hemoglobin A1c and the  
20 treatment level, that difference is greater than one  
21 percent. But that is not to state that the baseline  
22 of the treatment level and the endpoint at 16 weeks is

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1 greater than one --

2 DR. FLEMING: That's right, that's right.

3 DR. NEW: But what do we ask for? What is  
4 the difference we're asking for? Placebo to end  
5 treatment or baseline to end treatment?

6 DR. FLEMING: Well, the treatment effect is  
7 defined as the response at endpoint, or in this case  
8 using the last observation carried forward of each  
9 treatment group -- the difference between the two.

10 Now, in this case the placebo group actually  
11 went up, but that is as I mentioned, a fairly common  
12 finding when you do a controlled study in this  
13 population. So it's an issue for clinical design or  
14 clinical trial conduct, if you have a suspicion that  
15 the trial was done sloppily and that there was  
16 deterioration because of some systematic error in the  
17 conduct of the study.

18 But if it's simply a biologically explained  
19 phenomenon, that's you know, the kind of thing that a  
20 controlled study is designed to deal with.

21 DR. NEW: And therefore, the data that Dr.  
22 Sobel presented on the other drug represents the

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1 difference between placebo endpoint and drug end.

2 DR. SOBEL: Half of it. I gave you the  
3 straight drug effect and I gave you the placebo --

4 DR. NEW: The second part --

5 DR. SOBEL: The second part.

6 DR. NEW: -- represents the placebo drug --

7 DR. SOBEL: The placebo adjusted, right.

8 DR. NEW: Okay, thank you. Clear enough.

9 CHAIRMAN SHERWIN: But to remind you, there  
10 was a drug approved which did not reach that level  
11 that was planned -- .76 difference. So it's not an  
12 absolute requirement. As I understand it.

13 DR. FLEMING: That is absolutely right. And  
14 again, let me emphasize that our approach at FDA is  
15 typically to evaluate the absolute treatment effect  
16 and to try to ascribe a clinical benefit to that with  
17 which we can make a risk benefit assessment.

18 We do not make a direct comparison with  
19 other available therapies. That's very important to  
20 understand; that we can approve a drug that has an  
21 effect of .1 hemoglobin units if the benefit is  
22 justified by the risk. If it has negligible risk and

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1 yet you can show that kind of magnitude then you might  
2 -- you know, it seems highly unlikely, but you could  
3 approve such a drug.

4 CHAIRMAN SHERWIN: Dr. Sobel.

5 DR. SOBEL: I agree with what Zan is saying  
6 and that is, the reason in the case of acarbose we  
7 accepted -0.76 since this was really a drug the effect  
8 of which was non-systemic, so our risk benefit became  
9 a little bit more defined in favor of the drug,  
10 despite a relatively modest -0.76.

11 And Zan is quite correct; each case is  
12 judged by itself, and questions of systemic toxicity  
13 and more neuroendocrine effect such as Dr. Molitch was  
14 pursuing is certainly part of the judgment process.

15 DR. MARCUS: Would, on the other hand,  
16 things like triglycerides as ancillary data, also  
17 properly be judged?

18 DR. SOBEL: I think so. I think you're  
19 making a total judgment. The position of  
20 triglycerides, they're gradually moving over to  
21 accepting it as an independent risk, so it's not a  
22 radical thing. Two years ago I would have been more

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1 reluctant to talk about triglycerides.

2 CHAIRMAN SHERWIN: I just want to clarify  
3 one issue for myself. As I recall, the data was  
4 combined sulfonylurea and bromocriptine. The  
5 combination we clearly saw a reduction in  
6 triglycerides. In the monotherapy, was there no -- my  
7 understanding was there was no reduction.

8 DR. CINCOTTA: That's correct. The trend  
9 was in the exact same direction; slightly less  
10 magnitude but the P value did not reach statistical  
11 significance in monotherapy. It did reach statistical  
12 significance in both study K and study L.

13 CHAIRMAN SHERWIN: One thing that I just was  
14 wondering about. I know it passed by me among the  
15 slides so I may not have -- and I didn't pick up on it  
16 -- is, I know the drugs in the placebo group and the  
17 treatment group were comparable.

18 DR. CINCOTTA: That's right.

19 CHAIRMAN SHERWIN: What I'm talking about  
20 now is as of use. But were the doses looked at? I  
21 mean, I didn't know if I saw that data.

22 DR. CINCOTTA: Yes. We looked at the HbA1c

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1 effect as a function of sulfonylurea dose. We could  
2 show you that slide.

3 CHAIRMAN SHERWIN: Well, I was just curious  
4 whether --

5 DR. CINCOTTA: There was no effect on the  
6 sulfonylurea dose.

7 CHAIRMAN SHERWIN: -- the dose was different  
8 in the two groups.

9 DR. CINCOTTA: No. Roughly the -- we have  
10 also that data. The dosages of sulfonylureas was  
11 similar between the two groups.

12 DR. DAVIDSON: Was there a dose response on  
13 triglycerides? You know, in the bromocriptine arm?  
14 You know, the higher the bromocriptine the lower the  
15 trans --

16 DR. CINCOTTA: No, there wasn't.  
17 Unfortunately, we aren't in a position to really  
18 answer that question accurately, because 75 percent of  
19 the people titrated up to the maximum dose and we have  
20 such a small n number at 1.6, 3.2, that it doesn't  
21 allow for a statistical --

22 DR. DAVIDSON: And my other question -- you

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1 know, in the extension studies was triglyceride  
2 maintained at a lower level?

3 DR. CINCOTTA: We don't have that data.

4 DR. DAVIDSON: Because if --

5 DR. CINCOTTA: We didn't do any diurnals out  
6 in the extensions looking at triglycerides.

7 DR. DAVIDSON: The reason I think it's  
8 important is because you know, in your studies the  
9 best blood sugar is around four weeks, and then you  
10 see an increase in blood sugars in the fasting state  
11 after four weeks. And I wondered if triglycerides  
12 will have the same effect.

13 CHAIRMAN SHERWIN: Dr. Hirsch.

14 DR. HIRSCH: I have a sort of general  
15 problem; maybe the extension data can help me. but  
16 when you look at the data we have here in the book,  
17 the 24-week studies and so on, it's clear that this is  
18 still a dynamic thing. We haven't come to any stable  
19 position in this and obviously this drug is meant to  
20 be used over long periods of time, not just for 24  
21 weeks.

22 So for example, in many of these charts we

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1 could, you know, come up with the notion that very  
2 likely placebos -- which is sort of driven back to the  
3 baseline, whatever that placebo effect is -- looks  
4 like in many instances the Ergocet™ effect is coming  
5 up in the other directions of the baseline so that in  
6 general, however you wish to plot the final effect  
7 over very long periods of time, it would appear to  
8 diminish.

9           And I'm also trying to sort of understand  
10 this as Dr. New pointed out in relationship to the  
11 area under the curve with glucose. I need just a  
12 clarifying thing. In the study itself, how often was  
13 the area under the curve, all of the glucose  
14 parameters, studied? Was that every four weeks or  
15 something?

16           DR. CINCOTTA: No, it was not. The area  
17 under the diurnal curve from 7 a.m. to 7 p.m. was only  
18 analyzed and obtained at the beginning of the study  
19 and at week-24.

20           DR. HIRSCH: Just at the beginning and at  
21 the end of the study? So not during the study, so --

22           DR. CINCOTTA: We did not have every four

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1 weeks where the patients returned --

2 DR. HIRSCH: Okay, well here's now another  
3 problem that I have with this and that is, I know that  
4 in patients who are obese and have Type 2 diabetes  
5 triglyceride levels and glucosekinetics, for example,  
6 exquisitely sensitive to diet.

7 And it's exceedingly difficult to know  
8 what's happening with diet, and even though they're  
9 seen by a dietician periodically -- for example, the  
10 ratio of glucose to total calories in the diet or  
11 refined sugars, can be a very important determinant of  
12 what the triglyceride levels are.

13 And if in fact the carbohydrate intake  
14 percent goes up, triglycerides will go up or down  
15 accordingly. So I'm really wondering in an individual  
16 who's given a drug in the morning who may have some  
17 nausea or subclinical nausea, or tend to modify eating  
18 patterns, to what degree this happens -- specifically  
19 when you don't have the details of the glucosekinetics  
20 and that kind of thing, except at the very beginning  
21 and the end of very long periods of time.

22 So I'm not surprised about the difference

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1 between the AUC and the hemoglobin A1c because there's  
2 a whole, big block of time there that's really  
3 essentially uncontrolled experimentally, except to the  
4 extent that a dietician can do this in an outpatient  
5 setting -- which is not very high in our general  
6 experience.

7 It's poor, both in being able to do it as  
8 evidenced by the fact that you can't reduce fat people  
9 and treat Type 2 diabetes by diet very well -- this is  
10 why you're after the drug. And also the recall of the  
11 patients of what they've eaten is notably poor even  
12 with extended interviews and all kinds of instruments.

13 Can you comment on -- I mean, I guess I'm  
14 setting up as an alternative hypothesis that what  
15 happens here is you're giving people a mild nauseant,  
16 and everything follows.

17 DR. CINCOTTA: The nausea, as Dr. Paul  
18 pointed out, was very transient; really only high  
19 during the first few weeks of the study and  
20 thereafter, resolved to a very low level in the  
21 majority of the subjects in the study.

22 Secondly, when we looked at the treatment

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1 effect on HbA1c in subjects that experienced nausea  
2 versus the subjects that did not experience nausea,  
3 there were no differences in the HbA1c delta relative  
4 to the placebo group.

5 CHAIRMAN SHERWIN: So you have that data?  
6 That would be helpful, actually. Because that would  
7 be helpful to us, I think.

8 DR. HIRSCH: Just as one final -- the mere  
9 fact that the placebo people did what they did,  
10 suggests strongly that there's some kinds of major  
11 dietary, psychologic, whatever kind of non-drug  
12 effects going on in these people.

13 So I have no reason to believe the same  
14 kinds of effects are not going on in the others but  
15 are non-measured, since we can't explain what the  
16 placebo effect is and why it comes about that they  
17 suddenly become more unregulated for a period of time.

18 DR. CINCOTTA: The placebo group, you're  
19 speaking of?

20 DR. HIRSCH: That's correct. I mean, we  
21 don't understand that, so --

22 DR. CINCOTTA: Yes, right.

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1 DR. HIRSCH: Whatever happens in that also  
2 happens in the drug treatment group, plus the drug.  
3 And I'm trying to figure out that piece of it that was  
4 unexplained.

5 DR. CINCOTTA: Right. All I can say is that  
6 in fact, as Dr. DeFronzo pointed out earlier a variety  
7 of different trials with a variety of different anti-  
8 diabetic agents under the similar protocol design --  
9 Type 2 diabetics, obese -- clearly demonstrated in a  
10 vast majority of cases if not almost every case, that  
11 they see a placebo HbA1c rise from the baseline over  
12 the six month trial period.

13 And actually, if you do take a critical look  
14 at the numbers for several of them, that HbA1c rise  
15 was much larger than what we actually show in our  
16 studies.

17 CHAIRMAN SHERWIN: You know, I think mostly  
18 likely that phenomenon is related to the period of  
19 time that you lead into the study. Now, you recruit  
20 people for a period of time; they're enthusiastic and  
21 ready to go. You're really changing their mindset for  
22 a very brief period of time.

1           And I think if you have a long, lead-in  
2 period before the studies you'll see a very different  
3 pattern of response. So it has a lot to do I think,  
4 with behaviors around getting involved in clinical  
5 trials. I think that's --

6           DR. HIRSCH: How do you change the mindset  
7 to take less good care of themselves, or --

8           CHAIRMAN SHERWIN: Well people, when they  
9 get into a trial take care of themselves. They're  
10 being seen, they have a commitment. They don't know  
11 which drug they're on --

12          DR. HIRSCH: These people show -- the  
13 placebo group shows a deterioration of their --

14          CHAIRMAN SHERWIN: They do initially, and  
15 you see a drop during an initial phase, even probably  
16 in the last point before you start the trial. They're  
17 already in the trial emotionally, and so they're on  
18 their way down and then they come back to where they  
19 started out.

20          DR. PAUL: I believe this is the data you  
21 were asking for, relative to the relationship between  
22 nausea and response. And as you can see here, in

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1 Ergocet™ and placebo with nausea, the n's that we  
2 have right here, we didn't find any statistical  
3 significance.

4           However, if you look at the patients without  
5 nausea over on the far right here -- 285 of them  
6 totally going north -- obviously the nausea in and of  
7 itself really doesn't have the effect if you will, of  
8 providing a rationale of producing the better response.

9           DR. KATZNELSON: How about if you re-stratify  
10 that data looking for percent of patients who have A1c  
11 values changed by at least one percent -- with  
12 nausea/without nausea? How does that look? Do the  
13 patients who don't have nausea tend --

14           DR. PAUL: We don't have that data but we  
15 can certainly look at that.

16           CHAIRMAN SHERWIN: Thank you. That was very  
17 helpful. Dr. Critchlow.

18           DR. CRITCHLOW: Regarding the nausea, I  
19 think you made a comment that women tended to report  
20 more nausea and headache. Do you think that's due to  
21 women are more likely to report symptoms, or the  
22 greater absorption of the drug on women, or something

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1 else?

2 DR. PAUL: George DiSiperus? A comment to  
3 that, please?

4 DR. DiSIPERUS: I'm George DiSiperus from  
5 LRB Pharmacological Research. We did the  
6 pharmacokinetic studies for Ergocet™ and we did an  
7 analysis looking at the gender differences in  
8 absorption. And actually we found no relationship  
9 between area under the curve and body weight  
10 independent of sex.

11 DR. CRITCHLOW: I thought I saw somewhere in  
12 the briefing document that women -- there's a tendency  
13 for women to have greater absorption.

14 DR. PAUL: Actually, in the placebo group  
15 there was an increase in nausea in women over men as  
16 well.

17 CHAIRMAN SHERWIN: I was sort of surprised  
18 -- talking about gender -- that in each study there  
19 were more men than women; much moreso than I've seen  
20 in any of our other type 2 trials that have come  
21 through. Any explanation? Or is it just chance?

22 DR. PAUL: The sort answer is no, we don't

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1 have an explanation for that. We did indeed, practice  
2 what every other, I guess, investigator tries to do,  
3 and that is, we assuredly did not try in any way to  
4 bias the gender on entry into study.

5 CHAIRMAN SHERWIN: Dr. Molitch.

6 DR. MOLITCH: I don't know if we have an  
7 answer back from my earlier question. Do you have  
8 that on prolactin? Also --

9 DR. PAUL: Here they are.

10 DR. CINCOTTA: What we have graphed out here  
11 is the change over the 24-week treatment period  
12 measured at week-zero, week-8, and week-24 for fasting  
13 prolactins in these subjects treated with placebo and  
14 Ergocet™. And we have them for monotherapy and for  
15 adjunctive therapy.

16 The data are graphed as a delta from the  
17 baseline so let me just remind you that for these Type  
18 2 diabetic subjects that baseline was roughly nine to  
19 ten nanograms per ml. In other words, they were a  
20 little bit more elevated than what we see in the lean  
21 population --

22 DR. MOLITCH: Same in both sexes, or

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1 different?

2 DR. CINCOTTA: It was a little bit higher,  
3 actually, for the females, as you would imagine. It  
4 was like 12 to 13 nanograms per ml. And this is the  
5 delta and it's not separated out per sex, so this is  
6 a combination of female and male. And you can see  
7 obviously, for the placebo group there's no large  
8 difference over the 24-week treatment period.

9 However, for individuals on the Ergocet™  
10 you get approximately five nanograms which would bring  
11 them down into the five our six nanograms -- on  
12 average, between male and female -- nanograms per ml  
13 range. That's for adjunctive therapy.

14 For monotherapy it's the same situation.  
15 Actually, you see in both cases a slight trend toward  
16 the normal level. So again, the five nanogram drop  
17 from a mean at the start of around ten, is leaving  
18 them at around five nanograms per ml.

19 DR. MOLITCH: So that drop is 24 hours after  
20 the last dose of Ergocet™ which is supposed to be a  
21 shorter-acting drug than parlodel, is that correct?

22 DR. CINCOTTA: It has a quicker dissolution

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1 rate than parlodel and a faster absorption rate,  
2 therefore.

3 DR. MOLITCH: So that it's very likely that  
4 prolactin levels through the course of the day  
5 following the Ergocet™ over the next 8 to 12 hours,  
6 is probably very much substantially lower than this?

7 DR. CINCOTTA: Actually, let me get back to  
8 you again on that one. I think we do have them out  
9 later in the day, as well. So let me check that.

10 DR. MOLITCH: Yes, but it still raises this  
11 issue of taking a normal prolactin and lowering it to  
12 virtually undetectable levels for a substantial  
13 portion of the day and see what the potentially  
14 adverse effects might be of that.

15 DR. CINCOTTA: Okay, let's just review that.  
16 They're going down by five nanograms per ml. They're  
17 starting at the end of -- it's like four-and-a-half  
18 after 24 weeks -- and they're starting out at like ten  
19 --

20 DR. MOLITCH: That's 24 hours after the  
21 dose, so we'll have to see what your 24-hour curve  
22 shows.

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1 DR. CINCOTTA: Yes. It's similar.

2 CHAIRMAN SHERWIN: I understand that Dr.  
3 Steiner is about to leave, and so -- Roger, is your  
4 question lipid-related?

5 DR. ILLINGWORTH: Yes. Two questions. One  
6 is, did you -- since you showed that the drop in  
7 triglycerides was not surprising biggest in those with  
8 hypertriglyceridemia, if you looked at the correlation  
9 between change in say, fasting glucose or hemoglobin  
10 A1c and change in triglycerides, do the patients with  
11 the best improvement in the diabetic control get the  
12 best percentages in triglycerides? That's the first  
13 question.

14 CHAIRMAN SHERWIN: Anthony? The correlation  
15 between the change in glucose --

16 DR. CINCOTTA: No.

17 CHAIRMAN SHERWIN: -- and the change in  
18 triglyceride?

19 DR. CINCOTTA: No.

20 CHAIRMAN SHERWIN: No correlation.

21 DR. ILLINGWORTH: Which suggests a direct  
22 effect from low and free fatty acids in the event of

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1 glucose?

2 DR. PAUL: That's correct.

3 DR. ILLINGWORTH: The second question is,  
4 since you didn't measure liproteins by  
5 (unintelligible) did you measure alpha B as an  
6 indicator of LDL, VLDL particle number?

7 DR. PAUL: That was not measured on these  
8 studies.

9 CHAIRMAN SHERWIN: Yes, Dr. Simpson.

10 DR. SIMPSON: I'm just -- since we're  
11 talking about triglycerides, I was looking at the  
12 graph on page 63 of the handout, and I guess -- I may  
13 have got it wrong but I thought the claim was, you  
14 know, that it lowers the triglycerides and that's a  
15 good thing.

16 But looking at that and comparing it to the  
17 placebo which is just above it, it seems to me that  
18 there are an awful lot there who -- in both groups --  
19 that increased, and an awful lot who decreased it a  
20 small amount.

21 And then there are some in the placebo group  
22 who increased it a huge amount and some in the

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1 Ergocet™ group -- a few only -- who decreased it a  
2 large amount also.

3 And I just wondered if, you know, had some  
4 like, percentiles for those two so we could have some  
5 feel for what the real -- you know, how many for  
6 example, in both the placebo and the Ergocet™ group  
7 actually sort of were in the same range.

8 DR. CINCOTTA: The way you're describing the  
9 analysis we don't have it, but we do have something  
10 that's similar to that -- the categorical distribution  
11 of subjects that had triglyceride levels at study  
12 entry between 300 to 750, and then those above 750.  
13 That's as close as we could get to what you're asking  
14 for.

15 DR. SIMPSON: Because I mean, one  
16 explanation of your correlation for the Ergocet™  
17 group is that you've got some scattered out, a long  
18 way out from the main body of the data.

19 DR. CINCOTTA: Okay, so you can see here,  
20 for the individuals baseline triglycerides between 300  
21 and 750 nanograms per ml, obviously the n number as  
22 you pointed out, is decreasing compared to the total

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1 population, obviously.

2 But nonetheless, we still have 25 subjects  
3 within this category on Ergocet™ compared to 46 on  
4 the placebo. The delta there is roughly 200  
5 milligrams per deciliter and the statistical analysis  
6 shows a P value of .001.

7 Again, as you pointed out there are fewer  
8 and fewer subjects with severe hypertriglyceridemia  
9 greater than 750 milligrams per deciliter, but still  
10 the trend is still there and the relationship relative  
11 to the placebo group is still there. It's actually,  
12 even though the n number is small, still statistically  
13 significant.

14 DR. MARCUS: It seems to me that  
15 particularly in the ones who are higher than 750 that  
16 those are reasonably comparable to what you see if you  
17 use fibric acid derivatives in this same type of  
18 population. Is that correct, Jaime, or anybody who --  
19 we're in the same ballpark of triglyceride response?  
20 Okay, thanks.

21 DR. DAVIDSON: Can I ask another question?

22 CHAIRMAN SHERWIN: Yes.

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1 DR. DAVIDSON: You know, in your excursions  
2 from baseline, you know, the best effect of the drug  
3 was post-lunch. And you know, you lose some of the  
4 effect after dinner. And my question is, being a  
5 shorter acting bromocriptine, you know, will b.i.d. --  
6 have you tried in short studies what b.i.d. will do?

7 DR. CINCOTTA: No, no we haven't. We have  
8 no data giving it b.i.d.

9 DR. DAVIDSON: And my other question is, you  
10 excluded patients with diabetes that were beta  
11 blockers and diuretics in these studies. Will that be  
12 a contra-indication if this drug is approved, knowing  
13 that many patients with Type 2 diabetes and this, will  
14 be on small amounts of hydrochlorothiazide or  
15 colodiuretics?

16 DR. PAUL: I would like to give a rather  
17 full answer to your question in that you're starting  
18 to address the issue of drug-drug interactions,  
19 especially in the type of things that are given  
20 commonly in the diabetic population.

21 We did a very extensive program following  
22 the guidelines of the FDA toward the drug-drug

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1 interaction. We'd like to share that with you now.  
2 Dr. Kirk.

3 DR. KIRK: Good afternoon. I would like to  
4 review very briefly, an in vitro drug-drug interaction  
5 study that we completed on bromocriptine. In vitro  
6 drug-drug interaction studies are becoming an accepted  
7 way for anticipating or again to find potential drug-  
8 drug interactions before we actually enter the clinic.

9 But first just let me define what I mean by  
10 drug interaction, because there are several different  
11 types. Most clinically significant drug interactions  
12 are associated with the metabolic clearance of the  
13 drugs in the liver.

14 Typically a drug interaction results when  
15 drug A modifies the metabolic clearance of drug B when  
16 it's co-administered. These drug interactions occur  
17 in the liver which is the major site of drug  
18 detoxification, and is mediated by the cytochrome P450  
19 oxygenases almost entirely.

20 These potential drug-drug interactions can  
21 be evaluated very conveniently in vitro using human  
22 liver preparations. And this is becoming so important

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1 that the FDA has recently enunciated a guidance, which  
2 we have up here, entitled "Drug Metabolism, Drug  
3 Interaction Studies, and the Drug Development Process,  
4 Studies in Vitro". That was enunciated in April 1997.

5 The major focus of this guidance is to  
6 identify all the major metabolic pathways and the  
7 metabolites that are associated with the drug  
8 clearance in the liver. And of course to ultimately  
9 predict or identify potential drug-drug interactions  
10 that may occur with other current medications.

11 So what do we find? Encapsulated here are  
12 about three month's worth of work just to give you a  
13 flavor of what the metabolism of bromocriptine is all  
14 about. Well, it's a very old drug; it's been around  
15 since 1976. Its complete metabolism has really never  
16 been teased out until we did it recently.

17 But the indications were there that it was  
18 in fact, a 3A4 substrate. In fact, we find that it is  
19 metabolized exclusively by 3A4. It produces three  
20 major metabolites which are hydroxylated metabolites.

21 I want to point out the concentration here  
22 which is the Km of the reaction. The Km is the

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1 concentration of the bromocriptine which will actually  
2 drive the half-maximal enzyme rate. Just to give you  
3 a bit of perspective, this concentration here is  
4 approximately -- many, many orders of magnitude higher  
5 than the actual plasma -- peak plasma concentration of  
6 C max. I think it's the order of 80 picograms.

7 So that is you were to take this enzyme and  
8 put it at the level of the C max concentration, you'd  
9 essentially get no metabolism because of the  
10 inefficiency of the enzyme at such a low  
11 concentration.

12 Not surprisingly, it's also a potent  
13 competitor of this enzyme, which is not surprising  
14 since it is actually a substrate for it. Furthermore,  
15 it does not inhibit other major cytochrome P450s.

16 There are about five cytochrome P450s which  
17 metabolize about 85 percent of all drugs that are  
18 metabolized by -- if it's metabolized by P450 there's  
19 a greater than 95 percent chance that will be  
20 metabolized by one of these enzymes.

21 So by defining how bromocriptine interacts  
22 with these different isoforms we can sort of predict

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1 generally how it will interact with other current  
2 medications.

3 Also, at pharmacologically relevant  
4 concentrations it does not induce CYP1A or CYP3A4 in  
5 primary human liver cells, again at relevant,  
6 pharmacological concentrations. These are the two  
7 major inducible enzymes, and you can imagine that by  
8 modifying these enzymes you can certainly modify the  
9 clearance of other drugs that depend on these enzymes.

10 Finally, bromocriptine is non-toxic towards  
11 primary human hepatocytes at concentrations up to 100-  
12 fold -- the maximum plasma level. It could be higher  
13 than that. We just didn't go any higher at that  
14 point.

15 So what can we do with this information? We  
16 can make certain general predictions as to how they  
17 will interact with concomitant medications. And here  
18 we have some general predictions. We can predict that  
19 bromocriptine will not metabolically interact with  
20 drugs metabolized by non-CYP3A4 pathways.

21 For example, the sulfonylureas, they are  
22 metabolized through 2C9, so we can eliminate at least

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1 metabolic interactions with that class, which is  
2 important of course, since it is -- they were applied  
3 in the adjunctive therapy.

4 Bromocriptine will have no effect on the  
5 metabolic clearance of other CYP3A4 drug substrates.  
6 This is because the concentration of bromocriptine in  
7 the plasma is just too low to efficiently inhibit this  
8 enzyme and effectively inhibit the metabolism of the  
9 substrates.

10 Bromocriptine also, when it's co-  
11 administered with inducers of this enzyme activity, it  
12 would decrease bromocriptine plasma level. So there  
13 is a potential there for losing pharmacological  
14 activity, and you would have to readjust your dose.  
15 The inducer would of course, decrease your plasma --  
16 bromocriptine plasma level.

17 Also, this is the one that if you were to  
18 co-administer bromocriptine with substrates or  
19 inhibitors of CYP3A4 you would expect that the plasma  
20 level of the bromocriptine would actually increase.

21 Now, CYP3A4 substrates cover a wide area --  
22 broad, broad area of drug types, therapeutic types,

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1 and potentially -- or at least theoretically -- you  
2 could get interaction between bromocriptine and anti-  
3 infectives like ketoconizol, and so forth --  
4 erythromycin -- as well as calcium channel blockers.

5 But you must bear in mind that the  
6 concentrations of the actual bromocriptine is so low  
7 that this would counteract any potential increase in  
8 the bromocriptine that you would expect by the  
9 interaction.

10 In conclusion I'd just like to say that the  
11 metabolism of bromocriptine focuses on one metabolic  
12 pathway, and any drug interactions that occur would  
13 focus on that pathway. And there are two scenarios  
14 that we can picture.

15 One is, if you co-administer bromocriptine  
16 with an inducer of 3A4 you expect a decrease in plasma  
17 concentration of bromocriptine, where you'd expect a  
18 loss of activity and you'd have to adjust that with  
19 the dose.

20 The other scenario is where you would co-  
21 administer bromocriptine with substrative 3A4 and you  
22 would expect an increase. And this is where you would

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1 have to be careful. But then again, bear in mind the  
2 very low levels of bromocriptine present in the actual  
3 plasma would counteract any significant clinical  
4 effect.

5 Just let me underscore that these in vitro  
6 studies are exactly that; they're in vitro. they  
7 don't tell the whole story. There's no way that they  
8 can define the importance of these interactions at  
9 this time. But they are to be viewed as qualitative  
10 information.

11 CHAIRMAN SHERWIN: Dr. Sobel.

12 DR. SOBEL: Yes, I would just like --  
13 that's very nice doing the studies on, especially when  
14 the CYP3A4 is involved. You quite rightly said, it's  
15 a real pivotal area for the drug-drug interactions.

16 But I think the thrust of the questioning as  
17 far as drug-drug interaction would require an intact  
18 CNS. In other words, your exclusion, for example, of  
19 propranolol was based not on the metabolic  
20 consideration but a central nervous system.

21 And I wondered if you have any thoughts  
22 about the drug-drug interaction depending on dopamine

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1 and other CNS-acting -- where the most concerning at  
2 least, at this point -- at least as I gathered from  
3 the questioning. It's not an in vitro issue, it's an  
4 in vivo requiring an intact CNS.

5 DR. PAUL: We have not produced that data  
6 yet. We are thinking along those and many lines as in  
7 the future we go off and look to see how we do indeed,  
8 get along with the other drugs that are in this area.

9 I can share with you, of course, we've  
10 collected information now, the sulfonylureas which  
11 we're seeking the claim for. We are also involved in  
12 pretty late-stage work on metformin as one of the  
13 primary drugs that this might well be used with.

14 As far as the anti-hypertensive drugs that  
15 were allowed in the study, we can pick up on, in that  
16 short period of time -- the six month period of time  
17 -- certainly nothing with a signal to us that any of  
18 those drugs were interacting in any adverse way.

19 I do want to, if I may, return what happened  
20 as though we had Dr. Lachin up in the middle of an  
21 explanation and somehow that got turned, whether or  
22 not the panel would want to hear the rest of that

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1 explanation.

2 I think it's important because I think it's  
3 important to realize we have these three pivotal  
4 studies; that within the adjunctive studies and the  
5 monotherapy study we indeed did have a drop -- .5  
6 hemoglobin A1c -- reflective of the intent to treat  
7 analysis.

8 And that in the other parameters as well --  
9 triglycerides and free fatty acids -- we also have  
10 significant drops. And I don't want somehow that to  
11 be lost in the mix here.

12 CHAIRMAN SHERWIN: I think that's fair.  
13 John? Because this is obviously the key issue, how  
14 much of a drop is necessary for approval.

15 DR. LACHIN: Can I see slide 236, first?  
16 This is the pattern of changes in A1c in the  
17 adjunctive studies combined. You can see that there's  
18 an initial decrease and then a trend to rise in the  
19 placebo group; a much longer, sustained decrease in  
20 the Ergocet™ group, that also then, tended to rise.  
21 The patients started at an A1c of about 9.36.

22 Now let me see slide 385. All right, now if

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1 you look at the change in A1c that was observed in the  
2 placebo group -- I'm sorry, not the change. If you're  
3 looking for value of the A1c that was observed in the  
4 placebo group, the A1c at 24 weeks was 9.8, that A1c  
5 is associated with a risk of 6.57 per 100 patient  
6 years of sustained progression of retinopathy.

7 The patients in the Ergocet™ group at their  
8 level, which was 8.9 A1c, had a risk of 4.28 per 100  
9 patient years. And that is a 35 percent decrease in  
10 risk.

11 If I can have slide 386. Slide 386 shows  
12 the same thing. In the monotherapy group the A1c at  
13 the end of 24 weeks was 9.2 in the placebo group with  
14 a risk of 4.96 per 100 patient years. In the  
15 Ergocet™ group the A1c was 8.3 with a risk of 3.13  
16 per 100 patient years, which is a 37 percent decrease  
17 in risk.

18 Now, if you'd assume that the placebo  
19 patients would have been maintained at the baseline  
20 level and translate the average risk reduction -- if  
21 I could go back to slide 236.

22 If you assume that there was a horizontal

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1 line to the placebo group and that the line for the  
2 Ergocet™ group was consistently about .6 -- A1c  
3 percent lower than the average risk reduction, would  
4 again be on the order of about 30 percent.

5 So it's between 30 and 40 percent risk  
6 reduction that would be corresponding to this level of  
7 difference in the A1c.

8 DR. HIRSCH: For what period of time must  
9 that be sustained -- that difference -- to get this  
10 degree of risk reduction?

11 DR. LACHIN: Well, this is based on a  
12 follow-up of 6.5 years on average, in the DCCT. I  
13 mean, the DCCT data that I showed you a minute ago in  
14 the transparencies, quantifies the average,  
15 instantaneous risk over that period of 6.5 years. We  
16 did --

17 DR. HIRSCH: So there were repetitive  
18 measures during the 6.5 years that showed the mean  
19 reduction over 6.5 years?

20 DR. LACHIN: Right, right. So if these  
21 differences were to be maintained for an average of  
22 6.5 years then you'd expect to see between 30 and 37

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1 percent risk reduction in the risk of sustained  
2 progression.

3 DR. HIRSCH: Well, the reason I asked that  
4 specifically is, maybe Dr. Pian can help, together  
5 with you. She gave us two charts entitled,  
6 "Durability of Efficacy". And if I understand these  
7 two charts, the one that's labeled "Monotherapy", it  
8 looks like after 72 weeks or something, the story is  
9 over with, with Ergocet™.

10 Because it came right back to where it was  
11 before. So we'd have to redo this and divide it by  
12 some period of time that Ergocet™ -- did I  
13 misunderstand your chart?

14 DR. DAVIDSON: Dr. Hirsch, if you look at  
15 figure 3, change from baseline in the study K, the 24-  
16 week A1c is higher than the baseline. In study L the  
17 A1c --

18 DR. HIRSCH: I'm looking at the extension  
19 studies, because these are -- this is 72 weeks.  
20 That's big news to me; not the 24 weeks.

21 DR. FLEMING: The problem is --

22 DR. HIRSCH: Well, then could I just ask her

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1 to clarify? Is that -- am I interpreting that chart  
2 correctly? Does this mean that if you start taking  
3 Ergocet™ on zero weeks it goes down, and by 72 weeks  
4 it's exactly back to where you started from? Or am I  
5 misinterpreting the chart?

6 DR. FLEMING: Well, that is the case --

7 DR. HIRSCH: And the other one, too. Even  
8 with the adjunctive thing -- it looks like a sine wave  
9 or something, but it's averaging out to be nine.

10 DR. FLEMING: Well, the problem of course  
11 here, is that we don't have a control group. All the  
12 patients are, by that time in the extension, put back  
13 on therapy. And so this is the average of all  
14 patients who were --

15 DR. HIRSCH: I understand that, but do you  
16 understand also the plain meaning of this chart is  
17 that a group of people put on Ergocet™ at week-zero,  
18 and at week-72 they're at the same level they were at  
19 week-zero?

20 There was a nice dip for a period of time in  
21 between, but the thing is entitled, "Durability of  
22 Efficacy", and I'm concluding that there is no

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1 durability of efficacy --

2 DR. FLEMING: Well, that's the problem when  
3 you don't have a control group, and designing the  
4 whole --

5 DR. HIRSCH: Well, whatever -- there may be  
6 explanations for it, but I just want to make sure I  
7 got the facts straight.

8 DR. FLEMING: If we had had a control group  
9 we may have found that the same difference persisted  
10 to that point.

11 DR. HIRSCH: But when you tell me about risk  
12 then, and relating it to the DCCT, there's got to be  
13 a denominator here. There's got to be a time factor  
14 in this because this drug will only work for this  
15 period of time as far as we know. If we know anything  
16 else, I'd love to hear it from you.

17 DR. PAUL: Dr. Hirsch, I'd like to just  
18 offer you a different point of view. Dr. Rodgers,  
19 could you, from your statistical point of view, give  
20 us some guidance here?

21 DR. RODGERS: Right. Our company, Cyrix,  
22 has worked on much of the statistical analysis, and I

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1 think that is probably -- the essence has already been  
2 noted by Dr. Fleming -- but essentially it's very  
3 dangerous, it's extremely dangerous, it's even  
4 misleading, to implicitly compare the extension data  
5 with a "control group" that one might imagine.

6 Unless you would actually try to extrapolate  
7 from the control data per se. If you did that you  
8 would find a huge difference between extension for  
9 Ergocet<sup>TM</sup>-treated patients and extrapolated control  
10 from when the patients were in fact, randomized and  
11 not on medication.

12 It's important to understand that the  
13 patients were self-selected after 24 weeks, so you  
14 don't exactly know what's going on in terms of that  
15 selection process. It's important to note that the  
16 sample size is declining rapidly. It declines  
17 markedly after 24 weeks. It declines substantially  
18 more after 48 weeks so you have dwindling information,  
19 a higher degree of noise.

20 Things like how well the patient actually  
21 kept on their diet. They were extremely well  
22 monitored. During the placebo-controlled phase of the

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1 study that monitoring slipped dramatically once the  
2 extension was started. The extension was intended to  
3 basically look for a safety-type data, descriptive.  
4 It wasn't meant as a comparative trial.

5 And what I would say is that, without the  
6 placebo it would be dangerous to make too much along  
7 the lines of what is happening or what is not  
8 happening at that point.

9 I think that it's really important to  
10 remember that placebo-controlled trials answer a very  
11 basic question that I ask when I go to see my doctor.  
12 I'm not a physician but if I'm contemplating treatment  
13 I want to know, you know, how I would be if I were to  
14 be treated, and how I would be if I were not to be  
15 treated.

16 And that is the classical question asked by  
17 a placebo and answered by a placebo-controlled trial.  
18 That question is answered during the control phase.

19 DR. HIRSCH: No, but over the one year it  
20 probably is dangerous to assume this has lack of  
21 efficacy, but I would ask you, isn't there an  
22 equivalent danger to say that it is efficacious?

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1           You don't know either one; you don't know  
2           that it works and you don't know that it doesn't work.  
3           You just don't know anything in 72 weeks. Isn't that  
4           what you're saying?

5           DR. PAUL: For this particular dataset I  
6           don't think you can draw any real conclusion. I will  
7           tell you that --

8           DR. HIRSCH: So we don't know whether it  
9           works at 72 weeks?

10          DR. PAUL: We don't have controlled,  
11          longitudinal data out to 72 weeks.

12          DR. HIRSCH: You've answered my question.

13          DR. TESTA: I just want to address that  
14          issue a little bit what I think is more easily from a  
15          statistics point of view. What you're saying here is  
16          that in these studies, we start out at week-zero, you  
17          end up where you are at week-72 -- you end up where  
18          you left off at week-72.

19                 And therefore you say that there doesn't  
20          seem to be any effect of the drug -- that's what  
21          you're saying.

22          DR. HIRSCH: That's what the picture shows.

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1 DR. TESTA: Right, that's what that picture  
2 shows. And that's assuming that there was no  
3 deterioration beta cell function, there's no  
4 progression of disease, in fact.

5 Which we know, where these people would have  
6 ended up had they continued in the progression that we  
7 did see either in the adjunctive studies which is an  
8 increase of 1.8 percentage points increase per year,  
9 or in the -- and this is the group on placebo and  
10 Ergocet™ which is similar progression of disease  
11 implication -- or even on the monotherapy.

12 What I looked at here -- so that question  
13 comes off as the statistical problem in the masking of  
14 therapeutic effects. Here there's a duration of 6.25  
15 years and there's a progression of disease -- some  
16 sort of beta cell deterioration that causes an  
17 increase in HbA1c.

18 If you look at the monotherapy studies they  
19 are of less duration, 3.9, and that progression of  
20 that period of time is 1.0. If you look at the U.K.  
21 studies the progression in terms of HbA1c is, in newly  
22 diagnosed patients is .2.

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1           So I don't think one can say certainly, that  
2 these people here, there's no treatment effect,  
3 because if you were to do a projection, a simple  
4 projection, what you have here is an increase from 8.5  
5 where you would have expected them to go up at the end  
6 of the year-and-a-half.

7           So the effect that you see that they stayed  
8 down here, to me actually implies just the opposite;  
9 that there seems to be an increasing effect over time,  
10 because I would have projected that they would have  
11 ended up much higher if some sort of progression would  
12 go on. And that's a common phenomenon; that there is  
13 an increase in HbA1c in patients with Type 2 diabetes  
14 with an average duration of six to seven years.

15           DR. HIRSCH: Even with adjunctive therapy?

16           DR. TESTA: Yes.

17           DR. DAVIDSON: I want to go back. You know,  
18 I think the question that Dr. Hirsch asked is  
19 durability of action of the drug. You know, and if  
20 you go to page 16 in this booklet you're going to see  
21 all the studies, and actually only study L, you know  
22 -- well actually, the A1c at 24 weeks was the same as

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1 baseline.

2           You know, in every other study the A1c at 24  
3 weeks is higher than baseline. But Dr. New asked the  
4 question before; are we rating this drug based on what  
5 it does from baseline or what it does from placebo?  
6 You know, most of the effects after 24 weeks is not  
7 the effect of the drug, it's the effect of placebo.  
8 Because at 24 weeks it's either equal or worse than  
9 baseline.

10           DR. HIRSCH: I agree with you. Tell them,  
11 not me.

12           CHAIRMAN SHERWIN: Dr. Molitch.

13           DR. MOLITCH: I'd like to have Dr. Cincotta  
14 return. You may think I'm torturing you about  
15 prolactin -- maybe the audience -- but in fact, this  
16 has considerable relevance I think, to think about  
17 what is the mechanism of action of this drug.

18           Because if we think that its central effects  
19 on dopamine or other things and this really has very  
20 wide-ranging importance to other drugs that we use  
21 such as propaninol, and it has great importance for  
22 counter-regulatory hormones.

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1           It has great importance for other drugs that  
2 we know interfere with central catecholamine.  
3 Metabolism of the oxidase inhibitors, tricyclics,  
4 depressants, verapamil, other medications. And so  
5 that it actually is of quite considerable importance  
6 here as to what the mechanism of action of this drug  
7 is.

8           DR. CINCOTTA: One point at a time; the  
9 first point relating to the prolactin levels. And  
10 we've showed earlier that there was approximately a  
11 five nanogram per ml drop in the fasting levels, and  
12 what you came back and asked for were the post-  
13 prandial levels out through the day, which we have.

14           We have them both for monotherapy and for  
15 adjunctive therapy. And you can see that essentially  
16 it's the same story. Placebo group obviously there's  
17 no change relative to the baseline, but approximately  
18 a five nanogram per ml drop -- this is the post-  
19 prandial values -- these are averages of all six of  
20 those time points at 8, 9 a.m., 12, 1 p.m., and 6 and  
21 7 p.m. times.

22           Again, the delta is the same as the fasting.

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1 It's roughly five nanograms per ml in the monotherapy  
2 study and exactly the same -- five nanograms per ml  
3 delta in the adjunctive therapy studies. So overall,  
4 the point that you're addressing is what are happening  
5 in the prolactin levels over the course of the day.

6 On average, over the course of the day, it's  
7 a five nanogram per ml drop that these subjects are  
8 coming in --

9 CHAIRMAN SHERWIN: But that's really  
10 reflecting daytime when the levels -- before they  
11 begin to rise. The original hypothesis was that there  
12 was an alteration in the diurnal patterns so that  
13 prolactin remained elevated throughout the day.

14 DR. CINCOTTA: Right. And these --

15 CHAIRMAN SHERWIN: Whereas in people who had  
16 not -- that were obese, they had lower levels and then  
17 it rises about 10 o'clock at night and beyond. And so  
18 the question is, at 10 o'clock at night and beyond,  
19 what did prolactin do in this regimen? Do you  
20 normalize or do you just flatten out the prolactin?

21 In other words, the question that -- I'm  
22 sorry, Mark, maybe I'm asking the same question -- is

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1 whether you totally flatten out the curve and not  
2 restore the normal diurnal pattern, or do you restore  
3 the diurnal pattern?

4 DR. CINCOTTA: Okay, in our Phase 3 studies  
5 the only available data we have was measured from 7  
6 a.m. to 7 p.m.

7 CHAIRMAN SHERWIN: Right, I know that. I'm  
8 just trying to see other data that might give me an  
9 understanding of what the diurnal pattern would be  
10 with this kind of regimen. Even if it's not a Phase  
11 3 study.

12 DR. MOLITCH: The sustained effect -- oh,  
13 I'm sorry. The sustained effect that you see is  
14 actually quite remarkable with a single dose of a drug  
15 that's supposed to be more rapidly acting on the onset  
16 compared to parlodel.

17 So it raises the question as sort of pulse  
18 resetting that you've talked about. I mean, is there  
19 really a pulse resetting or do we have a sustained  
20 action on dopamine receptors centrally as well as on  
21 lactotropes? And I'd be interested to see the  
22 pharmacokinetics of Ergocet<sup>TM</sup> and blood as far as

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1 bromocriptine levels go compared to parlodel.

2 DR. CINCOTTA: Okay, again, take one  
3 question at a time. The levels of prolactin that  
4 we've measured in these studies from 7 a.m. to 7 p.m.  
5 If you measure it in -- we do have some smaller Phase  
6 2 studies and --

7 CHAIRMAN SHERWIN: In diabetics?

8 DR. CINCOTTA: In obese, non-diabetics but  
9 it's what we have available. And what you see is that  
10 nocturnal rise itself is blunted relative to the pre-  
11 treatment value as well. It's not obliterated,  
12 however, and so that you'd still have a delta from the  
13 diurnal to the nocturnal time periods of the day.

14 Secondly, the question relating to  
15 interaction with other drugs that influence central,  
16 mono-amine systems is another good question. We don't  
17 have drug-drug interaction data as you would well  
18 imagine, in even Phase 2 studies with this molecule.

19 However, the dosages that we are using are  
20 -- been compared to what have been used for example,  
21 with Parkinson's Disease, are lower. But the direct  
22 answer is, we do not have those drug-drug interaction

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1 studies to assess really, the CNS interactions in any  
2 legitimate way.

3 DR. MOLITCH: I understand that you don't  
4 have them, but it calls into question as to the  
5 importance of whether they will turn out to be  
6 important, if indeed this is the mechanism of action  
7 of the drug.

8 But how about your hypothesis that you find  
9 this sort of host of suppression of dopamine that then  
10 resets things? And here we see by looking at the  
11 prolactin levels is that you have a very sustained  
12 action without any kind of --

13 DR. CINCOTTA: Yes, there's a different --  
14 the CNS response, D<sub>2</sub> response to a D<sub>2</sub> agonist is  
15 different than what you see for the prolactin response  
16 to that same D<sub>2</sub> agonist. Generally, the bromocriptine  
17 binding at the lactatroph is very long and sustained.  
18 Actually, Michael Thorner published a lot of that work  
19 very early on -- maybe in the early '70s. I believe  
20 Mary Lee Vance may have also contributed to those  
21 studies.

22 But the bottom line was, at the lactotroph

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1 when you had bromocriptine -- and you can actually  
2 even do these studies in vitro with an isolated  
3 pituitary -- you see that the binding capacity there  
4 is very high and the effect is sustained. So that  
5 it's almost like an irreversible binding to some  
6 extent.

7 However, the dynamics in the CNS are  
8 somewhat different, and if you look at studies looking  
9 at classic D<sub>2</sub> responses to bromocriptine such as  
10 locomotor activity shifts in various rod-in models,  
11 those responses to one-time administration are not  
12 sustained over a 24-hour period, much the way that  
13 we're talking about for prolactin. So there is  
14 differences, so you can't extrapolate --

15 DR. MOLITCH: Or to extrapolate from the --  
16 to the human.

17 DR. CINCOTTA: Right. But I'm saying,  
18 within any given model there are differences in the  
19 responsiveness to bromocriptine, in the lactotroph  
20 versus the CNS. And that's all --

21 DR. MOLITCH: Do we have data on  
22 pharmacokinetics --

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1 DR. CINCOTTA: Yes.

2 DR. MOLITCH: -- of Ergocet<sup>TM</sup> compared to  
3 parlodel? Bromocriptine levels?

4 DR. CINCOTTA: We have Ergocet<sup>TM</sup>  
5 pharmacokinetics that we --

6 DR. MOLITCH: Compared to parlodel?

7 DR. CINCOTTA: Not compared to parlodel. We  
8 have Ergocet<sup>TM</sup> pharmacokinetics. Would you like to  
9 see -- do we have that?

10 DR. DiSIPERUS: There was a recent study  
11 done with parlodel. The rate of absorption of  
12 Ergocet<sup>TM</sup> is faster than parlodel. It appears in the  
13 blood faster.

14 DR. MOLITCH: Numbers? What kind of  
15 magnitude change? What are we talking about?

16 DR. DiSIPERUS: Well, in terms of magnitude  
17 change, the doses used were different but if you  
18 normalize the area into the curve for parlodels  
19 higher, about 25 percent higher, as well as the C max.

20 DR. MOLITCH: And the time to peak?

21 DR. DiSIPERUS: The time to peak is the  
22 same, but the rate of appearance is different.

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1 Ergocet™ does this, parlodel does that.

2 CHAIRMAN SHERWIN: This was a comparison?

3 DR. DiSIPERUS: No, no, it's not a  
4 comparison.

5 CHAIRMAN SHERWIN: So it was different  
6 investigators, different measurements, different  
7 patients --

8 DR. DiSIPERUS: The method of quantitation  
9 was probably the same.

10 CHAIRMAN SHERWIN: So we really don't have  
11 data for --

12 DR. MOLITCH: I think that some of us are  
13 skeptical, as you can tell, as to the mechanism of  
14 action of what we're seeing with respect to  
15 carbohydrate metabolism. And it seems like one very  
16 interesting, easy experiment to do to try to sort out  
17 the issue would be to compare once a day Ergocet™ to  
18 twice a day Ergocet™.

19 Because if you have the same, exact effects  
20 where you get an increased effect with twice a day it  
21 would suggest that perhaps this is some sort of  
22 peripheral mechanism rather than some resetting of

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1 what's going on.

2 If in fact you worsened the effect with  
3 twice a day then it would give credence to this  
4 resetting phenomenon.

5 DR. CINCOTTA: Let me address that question.  
6 We haven't run those studies in humans but we have run  
7 similar types of studies in animal model systems.

8 When one looks at the peripheral effects of  
9 bromocriptine on liver metabolism, hepatic glucose  
10 production, glucose oxidation, glucose turnover rates  
11 in liver, by a variety of techniques looking at the  
12 direct effect, or looking at the effect of  
13 bromocriptine on lipolysis in isolated adipocytes,  
14 nothing is found.

15 You can't give any direct effects of the  
16 molecule that explain the effects that you see when  
17 you give systemic administration of the drug.

18 Secondly, in animal model systems when we  
19 give the bromocriptine once a day instead of  
20 systemically, intracerebral ventricularly, one a day  
21 administration -- every day a pulse, one microliter  
22 into the ventricle of our animal model systems -- we

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1        elicit all of the effects that are seen with systemic  
2        administration of the drug.

3                When you put those two pieces of information  
4        together in our animal model systems at least, it  
5        strongly suggests that the drug is working centrally  
6        as opposed to peripherally.

7                DR. KATZNELSON:    Can I come back to this  
8        more regarding prolactin? I think it's important, not  
9        only from a mechanistic standpoint but also from how  
10       the dose is given, in that the comments are made in  
11       your writings here that with this dopaminergic  
12       hypothesis that maybe there's altered hypothalamic  
13       dopamine tone early in the morning to ascribe to the  
14       altered diurnal pattern.

15               Let me say again, I recently reviewed all  
16       this literature of obesity and I think it's hard to  
17       say really there is an altered diurnal pattern, and  
18       one of the papers that you've referred to here shows  
19       that there's maintained circadian rhythm when you take  
20       an obese individual but the aclophase has shifted a  
21       little bit to the morning.

22               But it's not really clearly documented that

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1 you find four to five times -- as you say here --  
2 increased prolactin levels during the daytime. I  
3 mean, I think there's -- some evidence suggests  
4 there's altered prolactin dynamics in these patients  
5 but I don't think it's hard data, particularly with  
6 your data using historical controls that we've all  
7 agreed already that that's hard to use in a control  
8 basis.

9 But you make the argument here that we want  
10 to give the dose in the morning because of this  
11 altered dopamine tone in the morning. That's one  
12 reason why to time it during the day -- in the  
13 morning.

14 And I want to come back to the fact that Dr.  
15 Molitch just brought up about using b.i.d. dosage. I  
16 think you may even have more efficacy if you gave it  
17 at different times of the day.

18 Our patients of hyperprolactinemia we only  
19 give it at nighttime. There's less dizziness, we get  
20 less nausea noted, they eat more meals, and you may  
21 have more efficacy. So I'm going to come back to  
22 other issues in a minute, but from a mechanism

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1       standpoint it's not so clear to me you need to give  
2       this in the morning.

3                   DR. CINCOTTA: Okay, your point's well taken  
4       about the prolactin levels in similar studies in the  
5       literature, however as you yourself pointed out,  
6       there are certain indications that the prolactin  
7       levels are in fact, elevated during the late portion  
8       of the day, and we in our studies certainly found that  
9       to be the case relative, again, I know by historical  
10      controls, weren't the best, but at that point in time  
11      we were going on published data where they had their  
12      own controls showing the increased prolactin levels.

13                   We were only using this to optimize the  
14      response to dopamine agonist that we believe is  
15      working centrally based on all the available evidence.  
16      There is not any evidence that we have in our  
17      possession that suggests even, that the drug is  
18      working peripherally. None.

19                   Secondly, when we did the experiments that  
20      were suggested of giving it twice a day in animal  
21      model systems, there's no difference whether we gave  
22      X milligrams per kilogram in the morning or split the

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1 dose up.

2 In our animal model systems the half-X in  
3 the morning and half-X in the afternoon, we really  
4 didn't see a change, an effect. You've got to  
5 understand here, when you're trying to elucidate a  
6 central mechanism of action where you're talking about  
7 the brain which itself is an exceedingly complicated  
8 system, it's a little bit more difficult than ordinary  
9 to tease out exactly everything that is happening.

10 However, along those lines I just want to  
11 make one additional point. With all the data that I  
12 showed this morning and elevated levels of  
13 norepinephrine and serotonin in the VMH and being  
14 reduced following the bromocriptine treatment and that  
15 being associated with improvement of the insulin  
16 sensitivity, hyperlipidemia, hyperglycemia, and the  
17 association of elevated levels of norepinephrine and  
18 serotonin -- in virtually every single animal model  
19 system published, without exception -- above and  
20 beyond all that if one takes these animal models,  
21 treats them with the bromocriptine to reduce that  
22 norepinephrine in the VMH and improve metabolism, the

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1 whole sequence of events can be blocked by  
2 simultaneous infusion, microinfusion of norepinephrine  
3 into the VMH. It blocks all the effects of the  
4 bromocriptine.

5 Therefore, when you put all -- I'm sorry,  
6 let me back up. It blocks nearly all the effects.  
7 It's not all, but it blocks a very large percentage of  
8 the effects. So that when you put all that  
9 information together it strongly suggests that the VMH  
10 is -- I'm not saying it's the only point for a target  
11 system, but it certainly represents a major portion of  
12 the response mechanism to the drug.

13 And it is one that is moving in the right  
14 direction towards what we see in the diabetic -- from  
15 what we see in the diabetic towards what we do see in  
16 the non-diabetic animal model systems. Obviously, all  
17 those experiments I just described are not amenable to  
18 human experimentation. So it is the way the situation  
19 stands.

20 CHAIRMAN SHERWIN: I think there are some  
21 things that are amenable in the sense that I think  
22 that's one of the problems we're facing as a committee

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1 is that the central nervous system does regulate  
2 metabolism but to a large extent does it through  
3 hormones and sympathetic activity.

4 And those hormones include growth hormone --  
5 cortisol, glucagon, catecholamines -- that are  
6 released from the adrenal medulla as well as locally  
7 within tissues, as well as (unintelligible). And most  
8 of those hormonal changes really mediate most of the  
9 metabolic phenomenon one sees, which are mediated in  
10 part, through the hypothalamus.

11 And the question that we're wrestling is, we  
12 haven't seen much of that data. We haven't seen  
13 growth hormone cortisol, glucagon, catecholamines, epi  
14 of any sort, and there is not clear evidence that  
15 insulin secretions affect it. And you only see an  
16 effect on insulin sensitivity at the very highest  
17 level of insulin that is higher than these patients  
18 would normally see.

19 So the question is, how is this working?  
20 And I think it would help us a lot if we had a better  
21 feel for how it worked. And I think some of that data  
22 could be done, you know, without having to do a long-

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1 term trial.

2 DR. CINCOTTA: Okay, your point is well  
3 taken. Let me try to address the neuroendocrine  
4 response to bromocriptine treatment as best that I can  
5 with the available data that we have now.

6 Okay, let's just take them one at a time and  
7 please permit me to use literature on some of this  
8 because it's the state of the situation as it stands  
9 right now.

10 Number one, as it relates to norepinephrine  
11 and sympathetic tone, in animal model systems and in  
12 humans -- and I know you're interested in the human  
13 situation. In humans the literature is filled with  
14 examples of studies where increased levels of  
15 norepinephrine in the blood have been reduced on  
16 bromocriptine treatment to levels that are seen in  
17 normal subjects.

18 And most of the situation here deals with  
19 hypertensive individuals. You take a hypertensive  
20 patient, you give them bromocriptine, you see a  
21 reduction of the hypertension, you see a reduction of  
22 the sympathetic tone, and you also see a reduction of

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1 the norepinephrine.

2 By the way, those are all three, common,  
3 pathophysiologies present in the diabetic population,  
4 getting back to Gerry Reaven's syndrome-X situation.  
5 So taking the available evidence -- we're  
6 extrapolating from it, admittedly, but it's all we  
7 have to work with as far as epinephrine goes -- we're  
8 reducing elevated levels of sympathetic tone, elevated  
9 levels of norepinephrine.

10 They are in fact, elevated in the diabetic  
11 population trying to bring them back towards what is  
12 seen in the normal population.

13 As it relates to cortisol, it's an  
14 interesting question and we have one slide on  
15 cortisol. There are not really any major change in  
16 cortisol in these subjects over the entire 24-hour  
17 period of the day.

18 This again, this is data from Gerry Reaven's  
19 study at Stanford. And you can see that, again the  
20 blue is before -- this is before and after eight weeks  
21 of treatment with bromocriptine -- before, after. And  
22 then yellow again, we threw in just for comparison,

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1 historical control groups -- historical control from  
2 the lean population.

3 Okay, so you can see that basically there  
4 are no major differences, first of all, between the  
5 historical normal and the before or after treated  
6 group here with bromocriptine. But if you focus just  
7 on before and after bromocriptine treatment, as far as  
8 cortisol is concerned there is not any real change in  
9 that diurnal pattern over the course of the day.

10 Let's now move to growth hormone that I  
11 alluded to earlier on and we got into that discussion  
12 of, is it going up, is it going down, is it good or  
13 bad. Okay, let's see what happens here with growth  
14 hormone.

15 Now, you remember for growth hormone, growth  
16 hormone is abnormally -- abnormally low in the obese  
17 population. Several studies have shown it and again,  
18 when we did our analysis out in Stanford we saw the  
19 same situation.

20 Here's blue, the before growth hormone  
21 levels during the course of the day, and then again,  
22 throwing in yellow here is what you generally see in

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1 the lean population. The levels are much higher over  
2 the entire 24-hour period during the day.

3 We check these individuals and treat them  
4 with Ergocet™ for a period of eight weeks. We see  
5 that there's an increase in growth hormone secretion  
6 that's predominantly associated with a nocturnal rise.

7 So as it relates to growth hormone and as it  
8 related -- similarly as it related to norepinephrine  
9 and sympathetic tone, there is a change but the change  
10 is towards normal. Away from the abnormal situation  
11 and it's moving towards what you see in the normal  
12 subject -- for growth hormone, for norepinephrine, for  
13 sympathetic tone, cortisol was normal to start with;  
14 there is not a real big change.

15 What else can I show you? Let's look at --  
16 we have some TSH -- T3 and T4 data --

17 DR. KATZNELSON: Excuse me. What doses of  
18 Ergocet™ were you were using --

19 DR. CINCOTTA: This was again, the same  
20 situation of 4.8, in the morning --

21 DR. KATZNELSON: This is the 4.8 dose?

22 DR. CINCOTTA: Once a day in the morning.

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1 If we now look at T3 and T4 -- I'm sorry, let's go to  
2 IgF-1 because we had talked about that earlier this  
3 morning; it was an excellent point.

4 Let's look at the IgF-1 levels in these  
5 subjects and see if anything remarkable is going on  
6 here and you can see that before and after treatment  
7 across the 24-hour period of the day for IgF-1, there  
8 isn't any real big change in these subjects.

9 I don't have a historical control maybe,  
10 actually to your pleasure on this slide, for  
11 comparison, but you can see clearly there is no change  
12 before and after for IgF-1.

13 So if we go now to the thyroid axis and we  
14 look at the T3 and the T4 levels in these subjects  
15 during the course of treatment, you'll see a similar  
16 situation. Here's T3 before and after treatment.  
17 There's not any real change in these obese -- these  
18 are obese, insulin-resistant subject.

19 And again, bromocriptine not doing anything  
20 remarkable here to T3 -- not at one timepoint -- over  
21 a course of the whole day as I've been showing for all  
22 these home profiles.

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1           T4 I believe we have, and it's a similar  
2 situation for T4. The before and after you see the  
3 levels are going up somewhat but you can see also the  
4 standard error bars on here are quite large. There's  
5 no statistically significant difference in T4 across  
6 the day.

7           What other hormones -- I don't have this for  
8 the prolactin. It's in the paper -- I believe it's in  
9 that paper, "Diabetes Care", but I can tell you what  
10 happened.

11           Glucagon we don't have. I wish we did have  
12 it, but let me -- for glucagon let me tell you what  
13 happens in our animal models. Again, start out with  
14 abnormally high glucagon levels in the OBOB mouse and  
15 we treat them with a dopamine agonist -- bromocriptine  
16 -- and we see that the elevated levels of glucagon are  
17 reduced to the normal level in the OBOB mouse model.

18           Again, the situation is the same as we're  
19 going through these hormone profiles in the  
20 neuroendocrine axis. If it's abnormal the drug moves  
21 it towards normal. If it's normal to start with it  
22 stays normal, and that's been the basic theme through

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1 every slide that we've shown.

2 I think TSH I also have so you can take a  
3 look at TSH as well. And TSH is interesting, and what  
4 we saw is this. Before treatment -- again, now here  
5 is our historical control found in yellow. Before  
6 treatment the levels of TSH are elevated.

7 Again, this is similar to what has been  
8 published by a few laboratories. This is a kind of a  
9 controversial area here -- what happens to TSH hormone  
10 levels in the obese patient. But clearly, this is not  
11 the first demonstration of elevated TSH in the obese  
12 population. There are a few other papers out there  
13 showing the exact same situation.

14 Again, after drug treatment, let's look at  
15 that TSH rhythm. Again, you can see that it is  
16 affected by the drug treatment, but the levels are  
17 affected in a favorable way. They're moving away from  
18 the abnormal towards what is seen in the lean,  
19 insulin-sensitive population.

20 So in all cases if they're normal they  
21 stayed normal; if they're abnormal they tend to move  
22 towards the normal, across the neuroendocrine axis of

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1 the available data that we've just reviewed, and  
2 including the literature with bromocriptine as it  
3 relates to the sympathetic nervous system and  
4 norepinephrine levels in the periphery.

5 Again, as it relates to that, because it is  
6 important, it is also important to realize that  
7 several studies have shown a linear relationship  
8 between increases in body weight and increases in  
9 sympathetic tone -- both in cross-sectional studies  
10 over time and in longitudinal studies.

11 If you look at any of the data in the Pima  
12 Indians from Eric Ravison out in Phoenix, Arizona,  
13 again, you see the same situation. Irv Shearer over  
14 in Europe publishes essentially the same phenomenon:  
15 increased sympathetic tone with increased body weight.

16 With drug treatment here we're decreasing  
17 sympathetic tone and you're decreasing insulin  
18 resistance.

19 So that's my long-winded answer to the  
20 question that you have on the neuroendocrine axis.  
21 Unfortunately, we didn't run through all these studies  
22 on our Phase 3 experiments, but in Phase 2 studies the

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1 available evidence shows that it's improving  
2 everything if it's abnormal, and we measured it.

3 DR. HIRSCH: In this connection it's worth  
4 remembering about autonomic tone. I think the  
5 preponderance of evidence now is that obese man has  
6 either normal or elevated sympathetic tone. It turns  
7 out actually, that parasympathetic tone, which also is  
8 measurable, is less.

9 But here's another point. When people lose  
10 weight, the moment they start losing there's a sharp  
11 decline in sympathetic tone, whether measured by  
12 turnover studies, 24-hour urines, perineal nerve, or  
13 a method that we use of heart rate variability.

14 And one of the things that most obesity  
15 people feel is that you'd like to increase the  
16 sympathetic tone when someone's losing weight rather  
17 than decreasing it; ergo -- I'm sorry, that's the  
18 wrong word to use -- hence, the beta 3 anergenic  
19 agonists and all kinds of efforts are being made now  
20 to enhance autonomic tone.

21 The general feeling is that if you want to  
22 get someone to lose weight you'd better either keep

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1 the sympathetic tone up or drive it up, and that  
2 stopping it or lowering sympathetic tone would be  
3 theoretically a bad idea. I'm not sure that this is  
4 based on a lot of knowledge, you understand, but at  
5 least it's one theoretical way of looking at it.

6 DR. CINCOTTA: I agree. Right. That's one  
7 theoretical way of looking at it. When you look at it  
8 in reality it's the opposite.

9 If you increase sympathetic tone, again by  
10 stimulating the VMH with noradrenaline or serotonin  
11 which actually potentiates the noradrenergic response  
12 in the VMH, those animals -- I didn't show it on my  
13 schematic -- they eventually induce insulin resistance  
14 as a function of the increased lipolysis and  
15 hepatoglucose output. But at the end of the  
16 experiment, at the end of four or five weeks -- and we  
17 just finished doing one of these studies last week so  
18 the data are very fresh in my mind -- they're obese.  
19 They're obese.

20 The point is that as you're increasing that  
21 sympathetic tone with that mechanism in the VMH and  
22 all that is entailed with it, there are other

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1 mechanisms that are also altered and changed and  
2 increased, and it may actually represent increase of  
3 parasympathetic tone.

4 So that you're just changing the steady  
5 state. You're burning and synthesizing X amount of  
6 fat following your manipulation in the VMH. You're  
7 now burning and synthesizing 4X amount of fat.

8 If you go again to my favorite model system,  
9 animals in the wild which represents a hundred million  
10 years of evolution, the increases in the body fat are  
11 associated with increased sympathetic tone, just as  
12 everyone publishes in humans and that you so clearly  
13 describe.

14 And it makes sort of sense, if you'll allow  
15 me to use that word, because these animals become fat  
16 for a reason, not so they can look fat. They become  
17 obese so that they can utilize that fat. And allow  
18 them to utilize that fat requires that you turn on  
19 sympathetic tone allowing from fat mobilization and  
20 oxidation.

21 Classically, in all the studies published in  
22 the literature -- whether it was a possum or a

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1 migratory sparrow or white-tailed deer -- increases in  
2 adiposity during the wintertime are also associated  
3 with increased oxidation.

4 It makes sense, for example -- I'm just  
5 going to pick one because I don't want to run on here  
6 -- but basically, for migratory animals, they put on  
7 an enormous amount of body fat for the migration  
8 because they use the body fat during the migration.

9 If you measure lipogenic rates and then you  
10 measure lipolytic rates during the migratory season of  
11 the year, they're both elevated. They are both  
12 elevated. And the same situation is what we see in  
13 humans.

14 If you look -- let me go to my little  
15 drawing board here -- if you look at any of the --  
16 don't cut me off now, Rich.

17 DR. PAUL: I wouldn't dare.

18 DR. CINCOTTA: One last graph. If you look  
19 -- the point that you made is an excellent one,  
20 because if you look at fat oxidation as a function of  
21 body fat in these animal model systems and in man, in  
22 human beings, that's the relationship. Fat oxidation

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1 increases as body fat increases.

2 If you then look at sympathetic nervous  
3 system tone -- we draw this like this and this like  
4 this -- again, you see a similar association; whether  
5 you ask Eric Ravison in his Pima Indian models or you  
6 go over to Europe and look at the data that's been  
7 accumulated there as well, it's the same story.

8 And they're all tied together. And what I'm  
9 saying is, you can influence them all simultaneously  
10 in part, by regulating what's happening in the VMH.  
11 Because by altering these VMH catecholamine activities  
12 you influence all three of them simultaneously.

13 CHAIRMAN SHERWIN: I have a question related  
14 to the points you're making and that is, these studies  
15 have been controlled so that diet has been regulated  
16 as best one could, I think. And so that there were  
17 little changes in body size in normal populations.  
18 And that helped us in many respects in interpreting  
19 data.

20 But my question is, in the free-wielding  
21 world, you know, that you're talking about here, and  
22 you just give the drug and you don't try to control

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1 diet at all, what would be the impact of the drug on  
2 body weight?

3 DR. CINCOTTA: Okay. Let me -- I'll --

4 DR. PAUL: Let me try to get out with a very  
5 succinct answer. We are looking at the issue of the  
6 impact on body weight. We do have an obesity study  
7 that is ongoing presently, right now, and that study  
8 will yield data in the not so-distant future.

9 As far as what we would expect, there's a  
10 certain body of science that suspects that weight  
11 loss, in and of itself, may stimulate the D<sub>1</sub> receptor.  
12 It may indeed, have an additional effect in and above  
13 that of the D<sub>2</sub> towards the overall, pharmacodynamic  
14 properties that we have seen metabolically.

15 So that's basically what we would expect.

16 CHAIRMAN SHERWIN: So you would expect  
17 people to lose weight, is that what you're saying? If  
18 they just took this drug independent of --

19 DR. PAUL: We don't have that --

20 CHAIRMAN SHERWIN: If I handed somebody a  
21 drug who's obese and didn't put him on a diet, saw  
22 what the effect was by itself, is that what the effect

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1 would be?

2 DR. PAUL: We don't have that data as yet.  
3 In addition to the study I mentioned to you, we have  
4 planned to --

5 CHAIRMAN SHERWIN: But theoretically, your  
6 hypothesis would be, it does promote --

7 DR. PAUL: It could be an outcome that would  
8 not surprise us if it happened.

9 DR. KATZNELSON: I imagine there would be  
10 data with parlodel on that --

11 CHAIRMAN SHERWIN: Well, that's what I was  
12 -- yes. That was my next question. You know, in  
13 terms of other -- you know, the long-term experience  
14 with bromocriptine. Is there such data out there?

15 DR. CINCOTTA: Retrospective analysis of  
16 individuals with micro- and macroprolactinomas treated  
17 with bromocriptine -- there is one review article on  
18 it and -- I'm sorry, let me take this back.

19 Retrospective analysis of individuals with  
20 micro- and macroprolactin illness had shown increase  
21 in body weight relative to the initiation of micro-  
22 and macroprolacintoma. But more importantly, in

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1 relation to your question, there are no data in the  
2 literature showing bromocriptine usage in the general  
3 population reduces obesity, number one.

4 However, there are several studies, I  
5 believe that clearly show that using a dopamine D<sub>2</sub>  
6 antagonist such as the phenothiazines for example, are  
7 clearly associated with an increase in body weight.  
8 I believe that that may be as close as we can get from  
9 the literature to answering your question.

10 CHAIRMAN SHERWIN: Dr. Molitch.

11 DR. MOLITCH: One question that I raised  
12 before which I didn't quite get an answer to is that,  
13 even if this -- whatever the mechanism of action is in  
14 prolactin levels don't reflect what you're trying to  
15 do, but nonetheless you do lower prolactin levels  
16 considerably in the normal range, down to actually low  
17 levels for individuals, what kind of side effects  
18 might we expect from lowering a normal prolactin level  
19 to a low prolactin level?

20 Have you looked for those kinds of side  
21 effects in reproductive system for example, or do you  
22 have other literature to bear to reassure us that

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1 nothing's going to happen?

2 DR. CINCOTTA: From the data that we showed  
3 you, basically the prolactin levels started out in  
4 that patient population in our Phase 3 studies at  
5 roughly ten nanograms per ml across the diurnal  
6 portion of the day when it was measured.

7 Following 24 weeks of treatment at 4.8  
8 milligrams it was lowered by, on average, five  
9 nanograms per ml. So it lowered it down to five  
10 nanograms per ml which is well within the normal range  
11 during the diurnal portion of the day.

12 As we discussed earlier, the information  
13 that I do not have for you is the nocturnal levels of  
14 prolactin. However, from our small Phase 2 studies it  
15 was also reduced as well, but it was not flattened out  
16 to be equivalent to the diurnal levels. There was  
17 still a considerable delta between the diurnal and the  
18 nocturnal level.

19 As far as association with any abnormalities  
20 and reproductive access, etc., we don't have any  
21 evidence of that in our Phase 3 studies and we don't  
22 have any studies that we've done to look at that

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1 specifically.

2 But really the answer is, the prolactin  
3 levels are not zero; they're five or six nanograms per  
4 ml.

5 DR. MOLITCH: But they're lowered  
6 considerably and I'd like to make sure the  
7 stromatogenesis was normal; that female reproductive  
8 access was entirely normal as well; that women were  
9 ovulating normally.

10 We know that in rats as you will, it's a  
11 glutiotrophic hormone. It's quite important for  
12 normal, reproductive function and lowering it may have  
13 some detriment. So I'm not reassured by your  
14 statement.

15 DR. CINCOTTA: That's the only available  
16 evidence I have to share with you today.

17 DR. KATZNELSON: A question about an  
18 alternative mechanism here. Doping receptors are  
19 present throughout the GI tract. Dopamine antagonists  
20 are used to treat gastric outlet problems.

21 And so the question here is, do you have any  
22 data that maybe some of the means for which the

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1 diabetes is improving its management has something to  
2 do with what the gut is seeing from the stomach?

3 DR. CINCOTTA: That's a great question.  
4 We've examined that issue in animal models. We didn't  
5 see any differences in absorption rates of any  
6 nutrients from the gut with bromocriptine treatment,  
7 number one. And secondly, getting back to our ICV  
8 administration of the drug, it was effective in  
9 producing all the effects that you see with systemic.

10 DR. KATZNELSON: So you don't know if  
11 there's any effect on gastric motility or gastric  
12 outlets on rates, by any means?

13 DR. CINCOTTA: No.

14 CHAIRMAN SHERWIN: Of course, you also could  
15 affect centrally, I mean, gastric. Dr. Critchlow.

16 DR. CRITCHLOW: A couple of questions. One  
17 is, I assume that people liken it to their hemoglobin  
18 A1c levels throughout the study, or during the 24-week  
19 period?

20 DR. PAUL: That is correct.

21 DR. CRITCHLOW: And the other is the  
22 responders. About 70 percent, 75 percent of

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1 individuals were titrated to the full dose. Was there  
2 any relationship to having achieved -- or taking a  
3 full dose -- to insulin -- to IV drop in hemoglobin  
4 A1c or to, or is some varied --

5 DR. PAUL: Yes, actually we did look at  
6 that data because it's an interesting point to see  
7 whether or not the responder group -- and the way I  
8 would look at that data -- whether or not there was  
9 more adverse events, i.e., nausea, that would have  
10 prevented one from reaching the maximum dose. We  
11 didn't see that.

12 DR. CRITCHLOW: But in terms of response,  
13 your efficacy variables, would that associate at all  
14 with taking the 4.8 dose as compared to a lower dose?

15 DR. PAUL: I think that the numbers that  
16 were involved in the controlled studies at the lower  
17 doses didn't really allow a good comparison for  
18 efficacy.

19 DR. CRITCHLOW: So that 20, 30 percent of  
20 the --

21 DR. PAUL: They were spread along various  
22 dose levels.

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1 DR. NEW: Perhaps you can help me to, I  
2 don't know, ratify or try to figure out what's  
3 troubling me. Dr. Cincotta began with a very eloquent  
4 presentation of how the ventromedial hypothalamus is  
5 a sort of, you know, master place that governs a lot  
6 of things, and if we could just dampen its influence  
7 on hormones you can get effects which are the  
8 objective of the study, which is to improve the Type  
9 2 diabetic.

10 Okay. But the problem I'm having is that  
11 though you did show an effect on carbohydrate  
12 parameters, on hemoglobin A1c, you haven't given me  
13 the body of evidence I would need to say that what  
14 you're seeing is working through the ventromedial  
15 hypothalamus.

16 Now, if you don't care what the mechanism is  
17 -- I mean, let's say that the objective of the study  
18 is to just help the diabetic who's Type 2, then it's  
19 a different objective from saying that you wish to  
20 show that what you accomplish is accomplished through  
21 a specific mechanism which involves the hypothalamus.

22 Tell me what you wanted to do.

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1 DR. CINCOTTA: We were trying to improve  
2 glycemic control in the Type 2 diabetic. There was no  
3 intent at doing anything or showing anything relating  
4 to mechanism of action in the human population. All  
5 our mechanistic studies were in animal model systems.

6 The human clinical trials were conducted  
7 with the primary, express intent of improving glycemic  
8 control and dyslipidemia and insulin resistance which  
9 we clearly showed we did do with the drug, in three  
10 independent studies.

11 And we were extrapolating the mechanism of  
12 action from our animal model systems because it is  
13 central -- and as I pointed out, it's not amenable to  
14 those types of studies in humans.

15 So we're not really running these studies  
16 with the objective of demonstrating mechanism of  
17 action in humans, but rather with the objective of  
18 demonstrating efficacy of improving their diabetic,  
19 hyperlipidemic condition.

20 DR. PAUL: And I believe we have done that  
21 repetitively, for both adjunctive and monotherapy.

22 DR. NEW: Okay, so the introduction that you

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1 gave, which is to introduce the experiments where you  
2 could infuse directly into the hypothalamus in  
3 animals, were only given to us to express the basis  
4 for your hypothesis?

5 DR. CINCOTTA: Correct. Correct.

6 DR. NEW: But not because it was your  
7 objective?

8 DR. CINCOTTA: Correct. Correct.

9 DR. NEW: Thank you.

10 CHAIRMAN SHERWIN: Dr. Sobel, just a quick  
11 question. The terms of guidelines that we played with  
12 recently, the length of study that is required for  
13 diabetes drugs -- because that relates to some of  
14 Jules' questions -- is six months?

15 DR. SOBEL: Yes. Well, I wouldn't want to  
16 hold the company to our direction we're moving now  
17 because, you know, the guidelines are evolving. We  
18 would prefer to see one-year data at least. But  
19 perhaps I'll ask the chief officer on guideline, Dr.  
20 -- oh.

21 DR. FLEMING: Obviously our guidelines are  
22 in development. And traditionally, we've required

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1 studies of at least three months. We've certainly, in  
2 the past three or four approvals, required six months.  
3 We would like to have experience extending up to a  
4 year for two purposes: number one, to assess safety,  
5 and number two, to have some sense about durability.

6 Now, obviously, this development campaign  
7 -- I mean, this development program began prior to any  
8 -- this began six years ago. And so I think it's a  
9 little unfair to apply an anticipated standard.

10 I would say that six months of efficacy data  
11 is adequate to establish the treatment effect. We  
12 would like to have some sense of the durability. And  
13 even in the proposed guideline, the idea we would do  
14 that by simply measuring the uncontrolled result at 12  
15 months.

16 And you see that that is in itself, not  
17 entirely satisfactory. You really do need a  
18 comparison group. This comes into an ethical issue  
19 about continuing patients for longer than a 3- to 6-  
20 month period of time on placebo.

21 And I think Dr. Hirsch was very concerned  
22 about this very ethical issue; that even he was

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1 concerned that three months might be too long to go in  
2 a placebo-controlled trial.

3 So you see we have some issues that we have  
4 to trade off here, and there is no completely  
5 satisfactory way to address all of them. But I would  
6 simply conclude by saying the company has performed  
7 studies of sufficient length for this committee to  
8 make some kind of judgment about the treatment effect.

9 Making the estimate of the treatment's  
10 durability is obviously difficult, but again, they  
11 have gone a long way to what we anticipate requiring  
12 anyway, in the guideline.

13 CHAIRMAN SHERWIN: Thank you very much.

14 DR. SOBEL: Just one more comment. It is  
15 still a judgment. I mean, if what we're seeing  
16 developing after 12 weeks is pointing to a durability  
17 result that troubles us, it's not important.

18 But I agree. We're not going to hold to any  
19 rigid, so-called guidance or guidelines because these  
20 are evolving, and the company chose a certain  
21 durability approach.

22 I think it's up to the committee to decide,

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1 based on what they see, do they suspect a reasonable  
2 durability or not? It's really a judgment based on  
3 the best data we have here.

4 CHAIRMAN SHERWIN: Thank you. Is there any  
5 -- I think we're -- Dr. Misbin.

6 DR. MISBIN: I just wanted to point out,  
7 although the guidance is evolving, as Dr. Fleming  
8 said, that despite what the ultimate form is we do  
9 actually have one year of data on all the other drugs  
10 that were recently approved. That would be acarbose,  
11 that would be -- antroglitizone, we have two-year data  
12 -- on repaglinide we have one-year data which you all  
13 saw.

14 Metformin was approved without one year's  
15 data. We only have six month's data in control  
16 trials, as I remember. Although of course, metformin  
17 had been used for many years in Europe and of course  
18 the U.K. study shows its durability of effect for many  
19 years.

20 CHAIRMAN SHERWIN: Okay. I think we've --  
21 I don't see any more questions. I'd like to go around  
22 the room just to have any final comments before we

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1 approach the questions. Thank you very much.

2 DR. HIRSCH: Maybe I can start the comments  
3 by saying, the answer to Dr. New's question about the  
4 relationship of the animal studies and the nature of  
5 the hypotheses underlying this, are not naught.

6 I mean, whatever your answer was that I  
7 might think was a well-taken answer, I think it helps  
8 enormously in evaluating the drug if there's a very  
9 clear, proven hypothesis of how it works and  
10 demonstration of its operating -- the mechanism in  
11 several animal species, because then, even though you  
12 can't do this as well in man for obvious reasons --  
13 you can't quite do the experiments as you can in  
14 animals -- there's a lot to recommend I think, the  
15 animal studies as a basis for what you're doing.

16 I fully agree with the answer that was  
17 given, that ultimately what we're really interested in  
18 is the efficacy of the drug in man. But to give us a  
19 lot of reassurance about the durability of it, safety,  
20 etc., it's wonderful to have a hypothesis that's been  
21 extremely well-tested in animals. So the two are  
22 clearly related, I believe.

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1 CHAIRMAN SHERWIN: Dr. Critchlow.

2 DR. CRITCHLOW: For me, given -- I see it,  
3 at least in the 24-week timepoint as showing a very  
4 modest effect. So in my mind it comes down to whether  
5 preserving the glycated hemoglobin level over some  
6 period of time will contribute to management of the  
7 disease if it's out there.

8 And that's -- to me, the issue is whether --  
9 we really haven't been able to assess that in terms of  
10 the durability of that, at least according to Dr.  
11 Lachin and DCCT, the hemoglobin A1c levels were  
12 relatively constant over the conventional group.

13 And if that's the case I'm not sure I see  
14 much of an extended -- hope of an extended benefit to  
15 these patients. But I can certainly be convinced  
16 otherwise.

17 CHAIRMAN SHERWIN: Dr. Katznelson.

18 DR. KATZNELSON: I want to emphasize what's  
19 been said about the importance of understanding the  
20 underlying mechanism here which really sounds like  
21 it's a roughly, black box.

22 I agree that probably at the end of the day

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1 was important to patients as to whether the medication  
2 works and has pretty significant results and that's  
3 going to feed down the line.

4 But I think it's important to have  
5 hypothesis-driven studies to demonstrate what the  
6 mechanisms are. We don't know if they'll be of use to  
7 us or not down the line. I think it would be. I'd  
8 like to know if there's any effects on gastric  
9 motility. I think that may have a clinically  
10 significant import.

11 So I think it would be worthwhile to follow  
12 through with further studies to kind of understand  
13 mechanisms underlying.

14 DR. ILLINGWORTH: I would certainly agree  
15 with the need to focus more on mechanisms in humans.  
16 I mean, I think it's valuable to extrapolate animals  
17 but it's nice to have the confirmation in man in  
18 clinical trial studies. So I think that's important.

19 The other thing is, the efficacy in terms of  
20 hemoglobin A1c goes down but isn't maintained, and so  
21 if you take individual patients who you don't have a  
22 control group, the data that's presented suggests

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1 that's about six months or thereabouts. You've lost  
2 most of your efficacy.

3 So I think there's a need to just get more  
4 data on longer term efficacy. Is that trend going to  
5 continue and how much of that is due to lifestyle  
6 variation, less the compliance to diet and all those  
7 kind of things, versus potentially loss of efficacy of  
8 the drug.

9 DR. NEW: I agree with what's been said  
10 before me, and I think that my own discomfort has to  
11 do with the fact that the drug has a known effect on  
12 the hypothalamus and many of the hormonal systems  
13 which the hypothalamus governs.

14 And that I can't be comfortable in thinking  
15 that the endpoint can be just the fat -- the glucose  
16 and the hemoglobin A1c -- because of the very  
17 widespread effect that these hypothalamically  
18 regulated hormones have on the body.

19 I must say that I would like to see data,  
20 not only on prolactin but on gonadatropins. I'd like  
21 to see more evidence that -- it's very confusing to me  
22 to see cortisol levels that are normal in the obese patient

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1 when I know the cortisol secretion rate is always  
2 increased in obesity.

3 I also know that growth hormone is usually  
4 suppressed in obesity, and I'd like to know what this  
5 drug does on the hypothalamus to alter those  
6 parameters. And then I might better understand the  
7 efficacy of the drug.

8 CHAIRMAN SHERWIN: Dr. Molitch.

9 DR. MOLITCH: I agree. I obviously have  
10 concerns about the mechanism of action of the  
11 mediation from a practical point of view; the side  
12 effects that may occur from lowering prolactin to  
13 lower than normal, as well as potential side effects  
14 that might occur via other drug-drug interactions that  
15 have action at the hypothalamic and pituitary levels.

16 And that we have relatively little  
17 information in this regard compared to the efficacy  
18 data which is modest but it seems real.

19 DR. MARCUS: I have fundamental agreement  
20 with what has been said. I think that I'd like to  
21 just focus on something a little bit different. I see  
22 patients at the VA Endocrine Clinic. They're

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1 generally obese Type 2 diabetics. They have powerful  
2 degrees of insulin resistance. They're usually on  
3 polypharmacy to manage their blood glucoses as well as  
4 to manage their lipoprotein abnormalities.

5 I have a great respect for the negative  
6 influence of triglycerides on health. In diabetic  
7 populations as early as the 1960s Margaret Albraith  
8 showed that triglycerides were the A-number-1  
9 predictor of peripheral vascular disease as well as  
10 coronary heart disease in Type 2 diabetics.

11 And so any medication that might achieve the  
12 dual purpose of lowering blood glucose and at the same  
13 time lowering triglycerides is something that would  
14 cause me to sit up and take notice.

15 I do have concerns about durability, and  
16 most of the evidence we've seen about durability today  
17 has focused exclusively on glycemic control. I would  
18 like to see more evidence with regard to durability of  
19 the triglyceride influence, as well as all the other  
20 markers of coronary and other vascular disease risk  
21 that we've talked about before, and on which data  
22 actually had not been presented to-date, or at least

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1 in this setting.

2 So I certainly would like to encourage  
3 additional work to explore those factors. I agree  
4 completely with Dr. Molitch on the idea that it seems  
5 to me that if you're wedded to a fundamental underlying  
6 mechanism of action, you then choose to ignore other  
7 strategies for drug delivery.

8 I think it was a mistake not to look at  
9 b.i.d. or t.i.d. or alternate forms of dosing with  
10 this medication because in fact, control of the  
11 important issues could have been much better, even  
12 though it would have flown in the face of the  
13 underlying theory about the ventromedial hypothalamus.

14 Finally, I think that although I was  
15 interested to hear that there was no direct effect of  
16 this medication in vitro on animal fat cells, if I  
17 understood this correctly, my limited knowledge of  
18 adiposite physiology is that the human fat cell is  
19 very different from the rat epididymal fat pad.

20 And there might in fact, be some direct  
21 effects on lipolysis that could explain some of the  
22 therapeutic effects that you've seen in people. So I

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1 would like to see some more clarification of that  
2 issue as well.

3 DR. SIMPSON: I think I agree with what's  
4 been said, and I think that the issue of whether the  
5 one dose is the way to go or not isn't clear. I mean,  
6 if you look at the diurnal graphs the pattern at the  
7 third meal doesn't duplicate the pattern at the --  
8 after they've had their dose, and it's different to  
9 the placebo. So the whole issue of how it's working  
10 is there.

11 CHAIRMAN SHERWIN: Dr. Davidson.

12 DR. DAVIDSON: One of the -- you know,  
13 patients with diabetes need new drugs. You know,  
14 we're not controlling it. And it looked initially  
15 very good because of the effect on triglycerides, but  
16 I need to agree with Dr. Marcus. We really don't know  
17 the durability on triglycerides.

18 And one thing that I really want to  
19 emphasize is, you know, most of your patients came  
20 from San Antonio, but the percentage of minorities --  
21 and I always -- I will keep dragging that to any study  
22 that is in diabetes -- one of every two newly-

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1 diagnosed patients with diabetes are minorities.

2 And you have a very small percentage of  
3 African-Americans in your study, and I think it is  
4 important to at least attempt, you know, and gear any  
5 study in diabetes to increase the percentage of  
6 patients of minority origin.

7 And one last point. If we look at the DCCT  
8 to compare any of these studies, we need to look at  
9 the DCCT today the way it is. You know, the DCCT,  
10 even the conventionally treated patients didn't go up  
11 from baseline. And the treated patients intensively  
12 went down two percent and were maintained for two  
13 years. We cannot compare apples with oranges.

14 CHAIRMAN SHERWIN: I have very little to  
15 add. I sort of came closest to Dr. Marcus' view. I  
16 actually -- when one looks at the data one has to take  
17 into account the fact that there is an effect, it's  
18 statistically significant, it's modest in magnitude,  
19 and we don't know how durable it is.

20 And so one of the things that I looked to  
21 was the lipid changes as something to hold onto, even  
22 though I didn't understand the mechanisms.

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1           The one thing that troubles me actually, is  
2           that the monotherapy did not show any significant  
3           difference in triglyceride. And so it required -- it  
4           looked to me almost, as if this had some better  
5           effects when you combined it with the drug that  
6           augmented insulin secretion than in situation where  
7           insulin secretion wasn't augmented in conjunction.

8           At least with respect to the triglyceride  
9           effect. Now that may fly in the face of what I think  
10          about insulin, but nevertheless I would have felt much  
11          more comfortable in terms of long-term durability if  
12          I knew that monotherapy had an effect on triglyceride  
13          levels.

14          Dr. Katznelson, you're not a voting member  
15          of this group; however, we would like your general  
16          thoughts before going to a vote. And we'll take each  
17          of the questions. Or, is that -- would you rather --  
18          how would you like to do this? General comment.  
19          Really about your general feelings, if you have any  
20          more, and then we'll kick off.

21          DR. KATZNELSON: I was asked to join the  
22          committee for questions regarding neuroendocrine

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1 mechanisms here, and I'd like to give my general  
2 thoughts on that.

3 As I said before, I'm somewhat concerned  
4 from a mechanistic standpoint of what this medication  
5 is doing. We really don't have a good feel for its  
6 effects, as Dr. New said, on other pituitary hormones  
7 such as gonadotropin release. We have some data on  
8 growth hormone in IgF-1.

9 But these hormones do have effects upon many  
10 aspects of the body and the role this drug has on  
11 effecting these different hormone systems is really  
12 unclear. I think it does have import, as was said,  
13 understanding these mechanisms on other potential drug  
14 interactions. So I think it would be important to  
15 delineate these further.

16 The side effect profiles that were described  
17 are pretty typical for what are seen for dopamine  
18 agonist bromocriptine, and are very limiting with the  
19 use of parlodel -- the nausea can limit many patients.  
20 And it sounds like that's not been a limitation here  
21 from the data the way it's been presented. I'd like  
22 to hear more about that.

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1           But my general feeling is, its modest,  
2 potential efficacy is there but I would like to see  
3 more information regarding the neuroendocrine  
4 mechanisms.

5           CHAIRMAN SHERWIN: Well, Thank you. So I  
6 guess we're ready to ask the questions.

7           DR. HIRSCH: Bob, would you define, in that  
8 first question, what the proposed population is, as  
9 you ask the question?

10          CHAIRMAN SHERWIN: I didn't ask the  
11 question, but I can -- the question is -- and then  
12 we'll get to what my interpretation would be: Are the  
13 study designs adequate to assess the efficacy and  
14 safety of the is drug for the proposed patient  
15 population?

16          Now, the proposed patient population, I  
17 think would have to be obese, Type 2 diabetics since  
18 those are the only patients that have been studied --  
19 as far as I can tell. Is that correct? That's the  
20 answer.

21          And with that question mind, Jules, why  
22 don't you start?

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1 DR. HIRSCH: No. I don't think the study  
2 designs are adequate to assess the efficacy of the  
3 drug, and I base this largely on a lot of the points  
4 of the discussion which had to do with my concerns  
5 about the relatively small change, the durability of  
6 that change, and that there may be explanations for  
7 that change that are peripheral to the action of the  
8 drug; namely dietary or lifestyle, or whatever.

9 So I would answer the study designs are not  
10 adequate to assess the efficacy of the drug for this  
11 patient population.

12 DR. CRITCHLOW: I would have to say no as  
13 well, and to add to that, in terms of the intended  
14 target population with respect to distribution by  
15 gender and ethnicity.

16 DR. ILLINGWORTH: No, also. I just don't  
17 think there's enough data on the longer term use or  
18 defined mechanisms -- particularly in long-term use,  
19 to say that it was going to be safe and effective  
20 after the longer time that it's been used.

21 DR. NEW: No, for the same reason.

22 DR. MOLITCH: Yes, I would also say no for

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1 the durability of the efficacy. I don't think the  
2 efficacy itself has been established. The safety I'm  
3 fairly concerned about, not knowing the effects of  
4 prolonged hypoprolactinemia.

5 DR. MARCUS: No, for the same reasons.

6 DR. SIMPSON: No, for the same reasons.

7 DR. DAVIDSON: No, for the same reasons, and  
8 you know, I would like to include minority patients.  
9 This is an obese population, I want to make the point.  
10 And Latino-Americans and African-Americans are the  
11 most obese in this country.

12 CHAIRMAN SHERWIN: I vote no. The second  
13 question is: What is the clinical significance of the  
14 reduced hemoglobin A1c levels observed in the pivotal  
15 studies?

16 We'll start with Dr. Davidson.

17 DR. DAVIDSON: You know, if we take it from  
18 baseline, obviously no. If you look at the data in  
19 this particular study, the average A1c at the  
20 beginning was nine percent. At the end was nine  
21 percent, okay? You go from placebo, you know, the  
22 average decline in A1c is .5 percent. Then I will say

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1 no.

2 DR. SIMPSON: I think that taking the  
3 definition of clinical significance that was given,  
4 it's there for a small group, but that's all.

5 DR. MARCUS: I think there's a potential,  
6 modest, clinical significance of the A1c itself, but  
7 I want to hold out the prospect for a much greater  
8 clinical significance for some of the other  
9 manifestations of metabolic control that are not  
10 addressed in this question.

11 CHAIRMAN SHERWIN: Dr. Molitch.

12 DR. MOLITCH: I think a delta of .5 percent  
13 is clinically significant so I will say yes.

14 DR. NEW: I say yes, and I think they have  
15 met the definition which was given to us as the  
16 difference between the placebo endpoint and the  
17 treatment endpoint of being greater than one.

18 CHAIRMAN SHERWIN: One percent?

19 DR. NEW: That was what the definition was.

20 DR. ILLINGWORTH: I would also say yes, but  
21 with the limitations that the data is only as good as  
22 it's been taken for the duration of the studies, and

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1 the studies aren't long enough.

2 DR. CRITCHLOW: I'd say the data show some  
3 efficacy for about 20 percent of the population.

4 DR. HIRSCH: I don't know quite how to  
5 answer. What is the clinical doesn't -- yes or no  
6 answers are not admissible to this but -- that's  
7 correct. So what I would say is the significance of  
8 the data are that they're sufficiently interesting,  
9 but I'm hopeful that further studies will be done to  
10 establish -- to give the data so that we can make a  
11 better judgment of the clinical meaning of this.

12 I don't believe they're sufficient for me to  
13 decide what the clinical significance is at this time.

14 CHAIRMAN SHERWIN: Based on the short-term  
15 data, I would say there's modest clinical  
16 significance. We have no long-term data and therefore  
17 it's almost impossible to actually decide what the  
18 clinical significance is. But it is a tease in the  
19 positive direction.

20 The next question is: What is the  
21 appropriate role of the prospectively defined  
22 responder analysis in the evaluation and/or labeling

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1 of this therapy?

2 DR. HIRSCH: Can you explain that to me? I  
3 don't know what that means.

4 CHAIRMAN SHERWIN: Dr. Fleming, I need you.

5 DR. FLEMING: You were given the responder  
6 approach and you could use that to influence your  
7 evaluation of efficacy, or you could say that it  
8 really can't be used for that purpose but might have  
9 some value in helping patients -- or helping  
10 physicians to select patients.

11 Or it might have no value at all. So those  
12 are the three major possibilities with respect to --

13 CHAIRMAN SHERWIN: The responder analysis is  
14 based on a drop in hemoglobin A1c of greater than .3  
15 percent over -- for or eight weeks? I forgot --

16 DR. FLEMING: Eight weeks.

17 CHAIRMAN SHERWIN: So that is the responder  
18 analysis. Subdividing patients to those patients that  
19 are responders versus non-responders based on that  
20 criteria.

21 DR. HIRSCH: I still don't understand it,  
22 but if I -- I think what you're asking me is, what's

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1 the role of what they told me today in the future, or  
2 something. Is that -- I think they ought to keep --

3 DR. FLEMING: If it helps you to understand  
4 whether the drug is efficacious or not, then that  
5 would be one response. If it doesn't help you then  
6 that would be the other major --

7 DR. HIRSCH: Well, since I have said no to  
8 question one, obviously it didn't help me to say yes.  
9 So the answer is no, it didn't help me to say yes. If  
10 that's what you want. I mean, I still don't  
11 understand it, but don't worry about that. There are  
12 many things I don't understand.

13 CHAIRMAN SHERWIN: Dr. Critchlow  
14 understands, I'm sure.

15 DR. CRITCHLOW: I found it interesting just  
16 to look at the positive predictive value of the  
17 response, although I'm not sure it helped me to come  
18 to a conclusion regarding the overall treatment  
19 efficacy.

20 DR. ILLINGWORTH: I think the data  
21 suggestion that some patients respond better than  
22 others is applicable for any drug, and one thing that

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1 I think could be done is to look at the good  
2 responders and the poor responders, particularly since  
3 we now know it's metabolized by the cytochrome P3A4  
4 system. Will the patients who are good responders on  
5 drugs that are known to go through that system, for  
6 example, or are there mutations in that that have been  
7 shown to affect metabolism of the drugs?

8 I think there are a lot of unanswered  
9 questions and so I think we just need more data.

10 CHAIRMAN SHERWIN: Maria. Dr. New.

11 DR. NEW: Yes, I'm not sure I understand the  
12 question either, but I want to say that the data  
13 presented today suggests that this drug may have  
14 efficacy but that more studies are required to  
15 determine that. And therefore, what I was told today  
16 did help me to think that this drug has potential.

17 CHAIRMAN SHERWIN: So the responder analysis  
18 you found useful --

19 DR. NEW: Yes.

20 CHAIRMAN SHERWIN: in terms of efficacy?  
21 It's a positive?

22 DR. NEW: Yes.

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1 DR. MOLITCH: I think it's actually quite  
2 helpful, and I'm sort of a believer in responder data  
3 like this. I think there are some people that respond  
4 to some drugs and some who categorically who do not.  
5 And I think it's worth separating those out at an  
6 early point in time.

7 But I'd like to see those to figure out why  
8 some responders don't respond and to get at the  
9 mechanisms of those responsiveness or lack thereof. And  
10 so I would say yes, the responder analysis does help  
11 me considerably.

12 DR. DAVIDSON: Dr. Marcus.

13 DR. MARCUS: I agree completely with Dr.  
14 Molitch.

15 CHAIRMAN SHERWIN: Wow. Dr. Simpson.

16 DR. SIMPSON: Well, I think the responder  
17 analysis can be useful in looking at a drug. I do  
18 think that it would have been particularly useful  
19 perhaps, to have taken that and to randomize those who  
20 responded to the other.

21 I'm not sure about the ethical implications  
22 about that, though. If you really believe the

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1 responders can you randomize them to placebo?

2 CHAIRMAN SHERWIN: Dr. Davidson.

3 DR. DAVIDSON: Obviously, there are two  
4 groups in the study for the responder analysis. One  
5 is those that use a dose of 1.6 milligrams, and 60  
6 percent of those patients were not responders. And  
7 then we have another dose that was the most widely  
8 used, which was 4.8 milligrams. And in that one, 70  
9 percent of the patients were responders.

10 To me, it did help me, but I would like to  
11 see entering, you know, more patients in between the  
12 1.6 and the 4.8.

13 CHAIRMAN SHERWIN: For me, the responder  
14 analysis did not help me with respect to efficacy.  
15 From a clinical perspective it could be useful if I  
16 understood why people responded. So I think that the  
17 approach of looking at the phenomenon is worthwhile  
18 from a clinical perspective.

19 From an efficacy perspective I don't  
20 consider it very useful. And I wouldn't use it in the  
21 analysis of whether it's efficacious enough.

22 Okay, number 4: Based on the efficacy and

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1 safety data presented, and your assessment of the  
2 overall benefits compared to the risks of  
3 bromocriptine therapy, do you recommend that this drug  
4 be approved for use in the proposed patient  
5 population?

6 Namely, obese, Type 2 diabetic patients.  
7 Dr. Davidson.

8 DR. DAVIDSON: Well, you know, one of the  
9 problems that I have is, we didn't address some of the  
10 important issues in this particular group of patients  
11 which is, you know, drug-to-drug interaction. and I  
12 really don't know the safety profile in its entirety.

13 And obviously, the benefits of the drug are  
14 minimal in lowering blood sugars. I think it's a new  
15 drug, it shows some promise, but at this point in time  
16 I will say no.

17 CHAIRMAN SHERWIN: Dr. Simpson.

18 DR. SIMPSON: I have some trouble in  
19 assessing the benefits in the sense that it, in the  
20 short term it seems that there is group who have their  
21 -- you know, the major endpoint reduced.

22 But there are some issues, it seems to me,

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1 with anything that affects the brain might effect the  
2 heart, and so on, which haven't been exactly  
3 addressed. So I'd say no.

4 CHAIRMAN SHERWIN: Dr. Marcus.

5 DR. MARCUS: Even though I'm going to say no  
6 to this question, I wanted to take the opportunity to  
7 thank Dr. Cincotta and his colleagues for one of the  
8 most stimulating and scientifically interesting  
9 presentations I've ever heard while on this committee.

10 My wife and I are currently at war with the  
11 white-tailed deer in our neighborhood, and I promise  
12 that in the future that I will see their plight with  
13 at least a little greater understanding, if not  
14 sympathy.

15 CHAIRMAN SHERWIN: Dr. Molitch.

16 DR. MOLITCH: No.

17 CHAIRMAN SHERWIN: Dr. New.

18 DR. NEW: I am going to say no but I really  
19 would encourage the sponsor to continue the study of  
20 this bromocriptine because I think it may prove to be  
21 of great interest. And I agree with Dr. Marcus that  
22 the presentations were very stimulating and excellent.

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1 CHAIRMAN SHERWIN: Dr. Illingworth.

2 DR. ILLINGWORTH: I'm going to vote no also,  
3 and I agree with the previous comments. I think the  
4 science that has been presented is excellent. We just  
5 need more defined data in humans and longer term data.

6 DR. CRITCHLOW: I'd have to say no, again  
7 for the same reasons.

8 DR. HIRSCH: No.

9 CHAIRMAN SHERWIN: I think I'm going to have  
10 to vote no, also. At the same time, you know, that's  
11 an area that is, I think, very important; namely that  
12 I think that the brain has a critical role to play in  
13 metabolism, and this is the first drug proposed to  
14 approach the problems.

15 Nevertheless, I think that if we saw a  
16 little stronger data we could have improved it on this  
17 go around. I think we need longer data to show  
18 durability before approval.

19 That's it. The last question we'll moot.

20 We're adjourned. Thank you, everyone.

21 (Whereupon, the Drugs Advisory Committee was  
22 adjourned at 4:12 p.m.)

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matter of:                   70<sup>TH</sup> MEETING

Before:                    ENDOCRINOLOGIC AND METABOLIC DRUGS  
                              ADVISORY COMMITTEE

Date:                      MAY 14, 1998

Place:                     BETHESDA, MARYLAND

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.

John Mongoven