

UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
ENDOCRINOLOGIC AND METABOLIC DRUGS  
ADVISORY COMMITTEE

MEETING # 68

WEDNESDAY,  
NOVEMBER 19, 1997

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The meeting took place in the Embassy Rooms I, II, and III, Bethesda Ramada Inn, 8400 Wisconsin Avenue, Bethesda, MD, 20814 at 8:00 a.m., Robert S. Sherwin, MD, Acting Chair, presiding.

MEMBERS PRESENT:

Robert S. Sherwin, MD, Acting Chair  
Kathleen Reedy, Executive Secretary  
José Francisco Cara, MD  
Cathy W. Critchlow, PhD  
Jules Hirsch, MD  
D. Roger Illingworth, MD, PhD  
Robert A. Kreisberg, MD  
Robert Marcus, MD  
Mark E. Molitch, MD  
Maria I. New, MD

CONSUMER REPRESENTATIVE PRESENT:

Jaime A. Davidson, MD

FDA REPRESENTATIVES PRESENT:

G. Alexander Fleming, MD  
Solomon Sobel, MD

SPONSOR REPRESENTATIVES PRESENT:

Martin Edwards, MD  
Jannie Fuhlendorff, PhD  
Barry Reit, PhD  
Frederick Reno, PhD  
Poul Strange, MD, PhD

ALSO PRESENT:

Richard Carr, PhD  
Wayman Wendell Cheatham, MD  
Peter Damsbo, MD  
Gerald A. Faich, MD, MPH  
Michael J. Fossler, PharmD, PhD  
Kurt Furberg, MD  
Kristian Hansen, PhD  
Dr. Nisben  
John Whisnant, MD

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

2 8:04 a.m.

3 ACTING CHAIRMAN SHERWIN: I'd like to  
4 welcome everyone. I think we have a quorum here and  
5 we'll begin. Hopefully, we have a few members that  
6 will be coming in probably in a few minutes. We'll  
7 move along and introduce them when they come.

8 I'd like to welcome you to this meeting  
9 of the Endocrinologic and Metabolic Drugs Advisory  
10 Committee of the FDA. The drug that we will be  
11 focusing on today is repaglinide from Novo Nordisk.

12 I'd like to begin by asking Kathleen  
13 Reedy to read the meeting statement which will be  
14 somewhat long, I suspect, today.

15 MS. REEDY: Conflict of interest  
16 statement for the Endocrinologic and Metabolic Drugs  
17 Advisory Committee, November 19, 1997.

18 The following announcement addresses the  
19 issue of conflict of interest with regard to this  
20 meeting and is made a part of the record to preclude  
21 even the appearance of such at this meeting.

22 Based on the submitted agenda for the  
23 meeting and all financial interests reported by the  
24 Committee participants, it has been determined that  
25 all interests in firms regulated by the Center for

1 Drug Evaluation and Research present no potential  
2 for a conflict of interest at this meeting with the  
3 following exceptions.

4 In accordance with 18 United States Code  
5 208(b)(3), full waivers have been granted to Dr.  
6 Mark Molitch and Dr. Robert Sherwin. A copy of  
7 these waiver statements may be obtained by  
8 submitting a written request to the Agency's Freedom  
9 of Information Office, Room 12A30 of the Parklawn  
10 Building.

11 We would also like to note that Dr.  
12 Jaime Davidson is excluded from participating in the  
13 meeting's discussions and vote regarding Prandin.  
14 Further, we would like to disclose that Dr. Robert  
15 Marcus' employer, Stanford University, has an  
16 interest in Eli Lilly, the manufacturer of several  
17 competing products to Prandin which is unrelated to  
18 the firm's competing products. Although this  
19 interest does not constitute a financial interest in  
20 the particular matter within the meaning of 18  
21 United States Code 208, it could create an  
22 appearance of a conflict. However, it has been  
23 determined notwithstanding this interest, that it is  
24 in the Agency's best interest to have Dr. Marcus  
25 participate in all official matters concerning

1 Prandin.

2 In the event that the discussions  
3 involve any other products or firms not already on  
4 the agenda for which an FDA participant has a  
5 financial interest, the participants are aware of  
6 the need to exclude themselves from such involvement  
7 and their exclusion will be noted for the record.

8 With respect to all other participants,  
9 we ask in the interest in fairness that they address  
10 any current or previous financial involvement with  
11 any firm whose products they may wish to comment  
12 upon.

13 ACTING CHAIRMAN SHERWIN: Now, normally  
14 at this point we have an open hearing and we  
15 entertain any statement from the audience regarding  
16 the product we're dealing with. Now, no one has  
17 come forth today for any statement from the public  
18 and I would entertain any right now.

19 If not, we will move ahead. Thank you.

20 Well, although I've stalled enough, I  
21 think what we'll do is begin by introducing the  
22 Committee. What I'll do is when those individuals  
23 who will join us in a few minutes, I assume, I'll  
24 introduce them as the time permits. So, perhaps we  
25 should begin with Dr. Hirsch who's behind the

1 machine that I can hardly see.

2 Why don't you introduce yourself?

3 DR. HIRSCH: Jules Hirsch, Rockefeller  
4 University, New York.

5 ACTING CHAIRMAN SHERWIN: Yes, please  
6 use the microphone.

7 DR. HIRSCH: Jules Hirsch, Rockefeller  
8 University, New York.

9 DR. ILLINGWORTH: Good morning. Roger  
10 Illingworth, Oregon Health Sciences University,  
11 Portland, Oregon.

12 DR. MARCUS: Robert Marcus, Stanford  
13 University.

14 DR. CARA: José Cara, Henry Ford  
15 Hospital, Detroit.

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

18 ACTING CHAIRMAN SHERWIN: Robert  
19 Sherwin, Yale University.

20 MS. REEDY: Kathleen Reedy, Food and  
21 Drug Administration.

22 DR. KREISBERG: Robert Kreisberg,  
23 Birmingham, Alabama.

24 DR. NEW: Maria New, Cornell University  
25 Medical College.

1 DR. FLEMING: Alexander Fleming in the  
2 Division of Metabolic and Endocrine Drugs, FDA.

3 ACTING CHAIRMAN SHERWIN: Okay. What  
4 I'd like to do is begin with Dr. Fleming. We'd like  
5 him to begin with some introductory remarks.

6 DR. FLEMING: Good morning, ladies and  
7 gentlemen. On behalf of Dr. Sobel and my colleagues  
8 at the FDA, we welcome you to this very important  
9 Advisory Committee meeting. Today, we will discuss  
10 repaglinide, a very promising oral therapy for type  
11 2 diabetes.

12 Repaglinide, like sulfonylureas causes  
13 insulin to be released from the beta cell. But  
14 unlike sulfonylurea therapies, repaglinide has a  
15 very rapid onset and offset of action. When taken  
16 immediately before meals, repaglinide therefore  
17 results in insulin secretory profiles that are more  
18 physiologic than sustained insulin released induced  
19 by sulfonylureas.

20 Repaglinide's major promise is that it  
21 may result in less serious hypoglycemia than longer-  
22 acting agents. Hypoglycemia, of course, is one of  
23 the major limitations of therapy with the currently  
24 available insulin secretagogues. Because of the  
25 potential of this drug to provide glycemic control

1 with the reduction in hypoglycemia, we ended a  
2 vision, identified the repaglinide NDA for expedited  
3 review. Since this is a new therapeutic approach,  
4 it is important that the Committee examine the  
5 available data as well as explore the ramifications  
6 of this approach.

7 I want to acknowledge the hard work,  
8 particularly because this did involve a priority  
9 review, of our primary reviewers: Mike Fossler,  
10 John Gueriguian, Herman Rhee, Baldeo Taneja and  
11 Xavier Ysern, and our consultant from the  
12 cardiorenal division, Mary Ann Gordon and her  
13 colleagues; and finally, our project manager, Mike  
14 Johnston who is a very important force in managing  
15 our effort.

16 I also want to thank the members of the  
17 Committee who continue to serve with distinction.  
18 Your willingness to add a third day to this meeting,  
19 occasioned by this expedited review, is an example  
20 of your dedication. Your participation is an  
21 extremely important part in FDA's drug evaluation  
22 process.

23 After the company presents an overview  
24 and we have an opportunity for general questions  
25 from the Committee, all of us -- that is, the

1 Committee, the company and the Agency -- will then  
2 engage in interactive discussions of several  
3 important issues. Committee members, of course, are  
4 invited to ask questions at any time, but they may  
5 want to defer questions that pertain to one of the  
6 interactive discussion points until we arrive at  
7 that point in the agenda.

8                   Once again, I want to thank you very  
9 much for being here. We look forward to the  
10 discussion today.

11                   ACTING CHAIRMAN SHERWIN: Thank you.

12                   I'd like to now introduce Mark Molitch  
13 from Northwestern who's joined us.

14                   I think we can go on with the  
15 presentation.

16                   Oh, Dr. Sobel, I almost forgot about  
17 you. Do you have anything you'd like to say? You  
18 weren't on my schedule, so I wasn't excluding you.

19                   Okay. Dr. Sobel just joined us.

20                   I'd like to begin then. We are a half-  
21 hour ahead of time and perhaps we can keep moving  
22 along at that rapid pace. So, I'd like to begin by  
23 having Barry Reit from Novo Nordisk begin his  
24 presentation.

25                   DR. REIT: Good morning Dr. Sobel, Dr.

1 Fleming, FDA members, Dr. Sherwin, Advisory  
2 Committee members, members of the press, colleagues  
3 and guests. My name is Barry Reit. I am vice  
4 president of regulatory affairs at Novo Nordisk and  
5 I am here to open the presentation of Prandin  
6 tablets, the first of a new chemical class of  
7 compounds designed to lower prandial glucose loads.

8 In 1984 and 1988, the ADA identified a  
9 need in the choices of oral hypoglycemic agents.  
10 They stated in the Physicians' Guide to Type 2  
11 Diabetes that in general, older patients have more  
12 renal failure and cardiovascular and hepatic  
13 problems as well as a tendency to skip meals and  
14 snacks. For this reason, it is best to choose an  
15 agent with relatively short duration of action which  
16 is less likely to cause profound hypoglycemia.  
17 Again in 1994, the ADA expressed the fact that this  
18 need continued by stating that severe hypoglycemia  
19 is the major complication of sulfonylurea therapy.  
20 Elderly patients as one subgroup are more  
21 susceptible to hypoglycemia, particularly when they  
22 have a tendency to skip meals or when renal function  
23 is impaired. It is within this context that  
24 repaglinide was developed for treatment of type 2  
25 diabetes.

1                   Repaglinide, the active drug substance,  
2                   is the pure S enantiomer of a highly substituted  
3                   benzoic acid derivative, a new chemical entity. It  
4                   has strongly pH dependent solubility and is highly  
5                   lipophilic. It was discovered in 1986 by Dr. Karl  
6                   Thomae, a subsidiary of Beringer Ingolheim. The  
7                   drug product is formulated from a spray dried  
8                   granulate with solubilizing agent and compressed  
9                   into tablets of 0.5 one and two milligram strengths.  
10                  The tablets have a pH independent dissolution  
11                  profile at pH 1 to 7 with a rapid disintegration and  
12                  dissolution rate.

13                  The proposed indication and usage for  
14                  Prandin tablets is as an adjunct to diet and  
15                  exercise to lower blood glucose in patients with  
16                  type 2 diabetes mellitus whose hyperglycemia can not  
17                  be controlled satisfactorily by diet and exercise  
18                  alone. The dose ranges from 0.5 to four milligrams  
19                  taken with meals to regulate meal related prandial  
20                  glucose load.

21                  The US Clinical Development Program  
22                  began in 1992 following submission of an IND. An  
23                  end of Phase II meeting was held in December 1994 at  
24                  which time initial demonstration of efficacy was  
25                  presented in US placebo control study 033. Five

1 one-year active control studies including US study  
2 049 were initiated worldwide and a six month US  
3 placebo control safety study, 065, and definitive US  
4 dose response trial 064 were planned. A pre-NDA  
5 meeting was held this past January, followed by the  
6 NDA submission at the end of June and granting of  
7 priority review in August. The safety update was  
8 submitted in October leading to today's Advisory  
9 Committee meeting presentation.

10 The remainder of our overview  
11 presentation this morning will be made by Dr. Jannie  
12 Fuhlendorff who will discuss pharmacology. Dr.  
13 Frederick Reno will present the preclinical safety  
14 section. Dr. Poul Strange will address clinical  
15 pharmacology and efficacy. Finally, Dr. Martin  
16 Edwards will discuss clinical safety.

17 Before I turn the presentation over to  
18 Dr. Fuhlendorff, I want to take a minute on behalf  
19 of my colleagues at Novo Nordisk and Beringer  
20 Ingolheim to thank the Agency for inviting us here  
21 to discuss Prandin. Additionally, I want to thank  
22 Dr. Fleming, Michael Johnston, the CSO, and all the  
23 FDA reviewers for their expeditious, supportive, and  
24 interactive participation throughout the review of  
25 the Prandin NDA. Open communication between Novo

1 Nordisk and the FDA has been an essential part of  
2 the timely review of this NDA and preparation for  
3 this meeting. We wish to thank you for all of your  
4 efforts.

5 DR. FUHLENDORFF: Thank you, Dr. Reit.

6 Ladies and gentlemen, I'm pleased to  
7 present to you this morning, the pharmacology of  
8 this new drug for type 2 diabetes.

9 Various preclinical pharmacology studies  
10 over several years have shown that repaglinide is a  
11 potent insulin secretagogue. Its mechanism of  
12 action is via the ATP sensitive potassium channel  
13 and it does not cause thymic exocytosis of insulin.  
14 It has distinct binding sites. The insulin  
15 secretion is glucose dependent and there's no  
16 secretion of insulin at sera millimolar glucose. In  
17 contrast to known effects of sulfonylureas,  
18 repaglinide does not inhibit proinsulin  
19 biosynthesis.

20 This first data slide shows the in vivo  
21 potency by blood glucose lowering in normal fed rats  
22 after oral dosing. The y axis is the change in  
23 blood glucose. Repaglinide in blue is 13-fold more  
24 potent than glyburide compared at the half maximal  
25 dose. The clinical dose of repaglinide is indicated

1 with a blue bar in the bottom and represents 2,320  
2 micrograms per kilogram.

3 The blood glucose lowering effect was  
4 studied further in fasted glucose loaded rats. The  
5 y axis is the plasmic glucose in millimoles per  
6 liter. The glucose loads are three, two, one, and  
7 .5 grams per kilo glucose. Please note that the  
8 repaglinide dose response is found over the range  
9 that includes clinical doses and note that the  
10 glucose level plateau at about three millimoles per  
11 liter or 45 milligrams per deciliter in rats.

12 The dose response for repaglinide was  
13 also demonstrated in fasted dogs as shown in this  
14 slide. Again, the y axis is the blood glucose in  
15 millimoles per liter. There's a dose dependence  
16 decrease in blood glucose in dogs from 10 to 1,000  
17 micrograms per kilo or one milligram per kilo.

18 The corresponding plasma insulin  
19 response is shown in this slide and the doses are  
20 the same as in the slides shown before. Please note  
21 the shape of the curve. There's a fast onset and  
22 decay over two to four hours after dosing. The most  
23 efficacious dose for insulin release is 300  
24 micrograms per kilogram in this model.

25 The pharmacological effects of our

1 insulin release is also shown in a rat model of type  
2 diabetes, the low dose streptosodazin model. The  
3 y axis is the blood glucose in millimoles per liter.  
4 Repaglinide in a dose of one milligram per kilogram  
5 is given a time serial and repaglinide decreased the  
6 blood glucose level from seven to four millimoles  
7 per liter 60 minutes after administration. The  
8 right panel show the plasma insulin in picamoles per  
9 liter. At the same time, the insulin level doubles.

10 The next series of slides shows the in  
11 vitro studies with this new chemical entity. First  
12 here, glucose dependent insulin secretion in  
13 perifused mouse islets. We compare equally potent  
14 doses at five millimolar glucose and that is 14  
15 nanomole of repaglinide and 200 nanomoles of  
16 glyburide. This shows a glucose dependent response  
17 with repaglinide and no secretion at sera millimolar  
18 glucose.

19 Repaglinide has a distinct binding  
20 profile in receptor binding studies. We were able  
21 to differentiate the sites in whole beta TC3 cells  
22 using two radioligands: first, radiolabeled  
23 repaglinide and second, radiolabeled glyburide.  
24 Further, we used four compounds as pharmacological  
25 tools and they are listed here. In order to

1 differentiate the sites, three binding sites were  
2 identified. First, a higher phenestitized for  
3 repaglinide with KD of 3.6 nanomolar and lower  
4 affinity for glyburide. This site is PPP  
5 insensitive. This site corresponds to the in vivo  
6 potency. The next two sites were PPP sensitive.  
7 The functional significance of these two PPP sites  
8 is not known.

9           The next slide more clearly demonstrates  
10 the differences. The  $IC_{50}$ 's, again in beta TC3  
11 cells, are listed here. Please notice this value.  
12 The  $IC_{50}$  for repaglinide on glyburide binding site  
13 is very high, equal to low affinity. We saw before  
14 that repaglinide was 13-fold more potent than  
15 glyburide in vivo in rats. Instead, the  $IC_{50}$  for  
16 the repaglinide binding sites reflect the in vivo  
17 rank order of potency as seen here. Sulfonylureas  
18 tolbutamide, gliclazide, and glipizide inhibits  
19 biosynthesis of insulin at low glucose concentration  
20 and might therefore exhaust the beta cell. There's  
21 no suppression biosynthetic activity with  
22 repaglinide at low glucose concentrations. This is  
23 the inhibition of proinsulin biosynthesis with  
24 sulfonylureas tolbutamide, gliclazide and glipizide  
25 and there's no inhibition with repaglinide.

1                   The direct exocytosis insulin was  
2                   examined in patch clamped mouse beta cells. Under  
3                   these conditions, there's no transport of potassium  
4                   through the ATP sensitive potassium channels and  
5                   there's no increase in intracellular calcium.  
6                   Sulfonylureas are able to release insulin by  
7                   stimulation of direct exocytosis. Two-thirds of the  
8                   insulin is estimated to come from this route. So,  
9                   clinical relevant concentrations of glyburide,  
10                  glipizide and tolbutamide cause direct exocytosis  
11                  and that is contrary to what is found with  
12                  repaglinide for which there's no exocytosis with  
13                  hundred nanomolar to 5,000 nanomolar.

14                  The direct exocytosis with the  
15                  repaglinide and glyburide is indicated here and  
16                  please focus on the right panel. On the y axis, the  
17                  increase in capacitance is indicated. The  
18                  glybentlomite or the glyburide curve is this one and  
19                  repaglinide is in the bottom here. So, no direct  
20                  exocytosis with repaglinide.

21                  To conclude, on the preclinical  
22                  pharmacology, repaglinide is a potent insulin  
23                  secretagogue compared to OHAs in fasted dogs, normal  
24                  rats, fed, fasted or glucose loaded rats. It acts  
25                  exclusively via the ATP sensitive potassium channel

1 in a tissue selective manner and does not cause  
2 direct exocytosis of insulin. Distinct binding  
3 sites exists. Repaglinide caused glucose dependent  
4 insulin secretion with no secretion at sera  
5 millimolar glucose. Repaglinide acts without  
6 inhibition of proinsulin biosynthesis. Finally, it  
7 is without peripheral effects or insulin  
8 synthesizing effects for which I did not show any  
9 data.

10 So, the pharmacological profile of  
11 repaglinide is a new chemical entity of benzoic acid  
12 derivative. It's an oral insulin secretagogue with  
13 distinct binding sites in the beta cells. There's  
14 no direct exocytosis and no suppressant of protein  
15 synthesis.

16 It's my pleasure now to turn the program  
17 to Dr. Fred Reno. Please?

18 DR. RENO: Thank you, Jannie.

19 Good morning. I'd like to summarize for  
20 you the rather extensive preclinical safety program  
21 that's been conducted on repaglinide that involves  
22 both safety pharmacology and toxicology.

23 With regard to safety pharmacology,  
24 approximately 16 studies have been performed to  
25 evaluate the potential for repaglinide to have

1 unanticipated pharmacological effects in other organ  
2 systems. At clinically relevant exposure levels,  
3 repaglinide failed to elicit any significant effects  
4 on central nervous system, cardiovascular,  
5 respiratory, gastrointestinal or smooth muscle  
6 systems.

7 Lagan binding assays such as possible  
8 effects on the N and L calcium channels and  
9 potassium channels revealed no inhibitory activity  
10 except for the effects on the ATP sensitive channels  
11 described by Dr. Fuhlendorff. Increases were seen  
12 in diuresis and sodium excretion at single doses  
13 that are 100 times the proposed clinical regimen.  
14 The multiple cardiovascular evaluations indicated  
15 that adverse effects have not been seen at  
16 intravenous doses of 1,000 micrograms per kilogram.

17 An extensive program of acute and  
18 chronic toxicity studies has been performed  
19 including carcinogenicity evaluation in two species  
20 and studies evaluating the potential effects on all  
21 aspects of the reproductive process. Teratology  
22 studies have been carried out in two species and a  
23 complete ICH compliant genotoxicity evaluation was  
24 performed as well as immunogenicity evaluations.

25 Chronic toxicological evaluations in

1 rats and dogs have been performed at duration  
2 treatments of up to one year. In the rat, the no  
3 effect dose is 16 milligrams per kilogram which  
4 results in plasma concentrations that are 38 to 85  
5 times the human exposure level. At higher doses,  
6 alkaline phosphatase levels are increased without  
7 histopathological effects. Dogs are sensitive to  
8 the hypoglycemic effects of repaglinide which is  
9 responsible for most of the effects in this species.  
10 At 50 milligrams per kilogram there were elevated  
11 hepatic enzymes with histological evidence of  
12 periportal enlargement with no evidence of  
13 hepatocyte degeneration. Thus, compared to the  
14 human dose of 0.32 milligrams per kilogram per day,  
15 there are no clinically relevant laboratory or  
16 histopathological changes.

17           The drug is not mutagenic in a battery  
18 of six genotoxicity studies. Four immunogenicity  
19 studies have revealed no evidence of immunologic  
20 responses or allergic reactions. In reproduction  
21 studies, repaglinide failed to produce an effect on  
22 fertility. It is not teratogenic when administered  
23 to rats and rabbits during the first trimester  
24 period of organogenesis. There is a developmental  
25 effect which is seen when the drug is administered

1 in late gestation and early lactation. I'll  
2 describe that in more detail later.

3 Carcinogenicity studies have shown no  
4 tumorigenic responses at doses that are more than 50  
5 and 100 times the clinical exposure level in males  
6 and females respectively. I'll discuss that more  
7 later, also.

8 In the reproduction findings, there are  
9 limb deformations that are developed in the  
10 offspring of females that are treated later,  
11 beginning with the third trimester of gestation.  
12 This was initially observed in animals that were  
13 eight to ten weeks of age with an observation of  
14 altered ability to walk correctly. It came about as  
15 a result of the behavioral evaluations that have  
16 been performed in these animals, an evaluation that  
17 is relatively new in preclinical development.

18 Subsequent studies have revealed that  
19 this effect is due to an altered structure of the  
20 limbs. Mechanistic studies that have been performed  
21 that have been designed to identify the specific  
22 period of effect have shown that this effect does  
23 not occur if the animals are treated in the first or  
24 second trimester, and is limited to the third  
25 trimester of gestation and the early period of

1 nursing. There is histological evidence of  
2 chondromalacia and an inhibition of the end growth  
3 of osteogenic buds.

4           Glucose levels are significantly reduced  
5 in maternal animals during this period of gestation  
6 and studies have identified that the offspring also  
7 have decreased glucose levels. Studies have  
8 identified that repaglinide can be transferred to  
9 the offspring via milk as evidenced by the fact that  
10 cross-fostering of offspring with untreated mothers  
11 also elicits this effect.

12           In summary, these are developmental  
13 changes as opposed to teratogenic effects and  
14 they've only been seen at doses that are significant  
15 multiples of the human exposure level and have not  
16 been seen at doses that are six times the human  
17 exposure level. In the carcinogenicity evaluation,  
18 repaglinide was not tumorigenic in the mouse at  
19 exposure levels that run from 71 to 160 times, 169  
20 times the human AUC in males and females.

21           This is a bar graph in the rat  
22 carcinogenicity study that describes the exposure  
23 margins for the four treatment groups of males and  
24 females. I call your attention here. These numbers  
25 at the top of the bar graph represent the multiples

1 in excess of the human AUC that resulted from the  
2 exposure of animals at these four doses. I point  
3 out to you that in this study at these two doses  
4 here, the two lowest doses, which represent 51 and  
5 in excess of 100 times the human exposure level,  
6 there are no tumorigenic effects.

7           There is at the doses that result in 90  
8 to 200 times the human AUC, an increase in benign  
9 thyroid tumors in the males. It's interesting to  
10 note that these benign thyroid tumors were not seen  
11 in the females even though the females' plasma  
12 concentrations were significantly higher than those  
13 of the males. At the very highest dose only that  
14 results in a 200 fold margin of the human AUC, there  
15 is an increase in the spontaneous rate of benign  
16 liver tumors in these male animals. It is again  
17 interesting to note that females who were exposed to  
18 higher plasma concentrations of repaglinide at that  
19 same dose, these tumors did not develop. This tumor  
20 type spontaneously occurs in rats and in this study  
21 were only seen at an increased incidence.

22           A study was done to elucidate the  
23 mechanism for the development of the thyroid tumors  
24 in the male rats. It was identified through these  
25 studies is that animals that are treated at those

1 two higher dosage levels develop a decrease in  
2 plasma T3 levels. The decrease in the plasma T3  
3 levels result in increased levels of TSH and that  
4 results in an enhanced proliferation within the  
5 thyroid gland. That phenomenon of the increased TSH  
6 resulting in an increase in proliferation is a known  
7 phenomenon that has been seen with other drugs such  
8 as phenobarbital and some of the phenothiazine  
9 antidepressants. The current state of knowledge  
10 would suggest that that mechanism is not comparable  
11 to anything that is seen in humans. In the clinical  
12 program that will be described later, there were no  
13 changes in T3 uptake, T4 or TSH levels during the  
14 clinical program.

15 So, with regard to the conclusions from  
16 the carcinogenicity evaluation, we can say that  
17 repaglinide is not genotoxic. That there is a high  
18 exposure safety margin within these studies. That  
19 the development of the thyroid tumors is a mechanism  
20 that is specific for rats. That the mouse  
21 carcinogenicity study is negative and the conclusion  
22 would be that there is no clinical risk as a result  
23 of this information.

24 With regard to non-clinical  
25 pharmacokinetics, repaglinide in all of the animal

1 species study is rapidly absorbed with peak  
2 concentrations achieved in less than one hour. The  
3 drug is highly bound to plasma proteins exceeding 95  
4 percent in all species examined. That in rodents,  
5 plasma levels in females are two to three times  
6 higher than those seen in males and that is a  
7 situation that is frequently seen in rodent studies.  
8 The drug is highly excreted by the bile with only  
9 eight percent of radiolabeled repaglinide excreted  
10 in the urine. The drug is metabolized by  
11 glucuronidation and/or oxidative pathways within the  
12 liver. The metabolite profile in the preclinical  
13 species are similar to those seen in man.

14 In conclusion, the preclinical safety  
15 assessment of repaglinide has shown a favorable  
16 safety profile with no suggestion of potential  
17 adverse toxicity at clinically relevant doses.  
18 That's described on the enhancement of the slide  
19 that was shown to you by Dr. Fuhlendorff.

20 Now I'd like to introduce to you Dr.  
21 Poul Strange who will discuss with you the clinical  
22 pharmacology and the clinical efficacy of  
23 repaglinide.

24 DR. STRANGE: Thank you.

25 As in animals, repaglinide is rapidly

1 absorbed and eliminated in man. Depicted on this  
2 slide is a pharmacokinetic profile comparing oral  
3 solution with a tablet. Note the T<sub>max</sub> at 45 minutes  
4 and the rapid elimination. Note also that the  
5 tablet is virtually identical to the oral solution  
6 profile demonstrating the in vivo correlate of the  
7 rapid dissolution of the repaglinide tablets. The  
8 levels of drug and plasma after these things are  
9 generally in the level of 10 to 15 nanograms per ml.  
10 So, it's rapidly absorbed from the gastrointestinal  
11 tract. T<sub>max</sub> is unchanged by food. There's a  
12 marginal decrease in AUC with food. It is rapidly  
13 eliminated from the bloodstream with a half-life of  
14 one hour. High clearance, 38 liters per hour and  
15 other PK parameters are listed below.

16                   Sixty percent of the plasma  
17 concentration at any time point is parent compound.  
18 There are no chiral conversion in vivo. Repaglinide  
19 is primarily metabolized by a cytochrome P450,  
20 isoform 3A4. None of the metabolites contribute any  
21 significant activity. Ninety percent of the dose is  
22 excreted in the feces via biliary secretion. The  
23 major metabolite found in feces is a dicarboxylic  
24 acid which is inactive. Eight percent is excreted  
25 in the urine as metabolites. Of those eight

1 percent, less than one percent is parent compound.

2           Already in early clinical studies in  
3 type 2 diabetes patients, the rapid absorption and  
4 elimination of repaglinide was confirmed with  
5 clinical use. In this study, patients were given  
6 meals at 8:00, 12:00 and 6:00 p.m. This is really  
7 8:00 in the morning. What is seen is that the  
8 repaglinide profile shows a rapid increase and a  
9 rapid decrease down to almost baseline levels.

10           On the next slide, the simultaneous  
11 insulin profiles are demonstrated. In the left  
12 panel for your reference is repeated the previous  
13 pharmacokinetics slide. On the right panel, the  
14 insulin concentrations in plasma are shown. The  
15 dashed line here is the baseline value in response  
16 to the three standardized meals. The solid line is  
17 the insulin response to the same standardized meals  
18 given with the dose of repaglinide. Note here that  
19 the peak is increased and that the insulin secretion  
20 declines down to the levels seen with the normal  
21 insulin response to the meals in these type 2  
22 patients.

23           On the next slide, I'll show you the  
24 simultaneous glucose profile. And again, I've  
25 repeated the repaglinide PK profile and the insulin

1 profiles for reference. The glucose curves are  
2 shown here with the dashed line being the baseline  
3 value without repaglinide treatment and the solid  
4 line being the glucose concentrations with time with  
5 repaglinide treatment. Note the substantial  
6 decrease in glucoses. The average 24 hour glucose  
7 in this trial decreased from about 190 milligrams  
8 per deciliter to about 130 milligrams per deciliter.

9           Subsequent to this, dose ranging and  
10 dose tolerance trials investigating the dose range  
11 from .125 all the way to 20 milligrams preprandially  
12 to each meal was investigated. Based on those data,  
13 those response trials was designed and I'll describe  
14 that in some detail. Patients with type 2 diabetes,  
15 either naive to oral hypoglycemic therapy or  
16 previously treated with oral hypoglycemic therapy  
17 went through a screening and went through a two to  
18 three week stabilization period without drug.  
19 Patients that after that stabilization period had  
20 fasting plasma morning glucoses between 180 and 300  
21 were then randomized to either placebo or five dose  
22 levels of repaglinide given preprandially with each  
23 meal. Doses were taken 15 minutes before each of  
24 the three main meals.

25           Patients were confined to a hospital

1 unit in weekly 58 hour stays, during which they  
2 received the same set of standardized meals at every  
3 of those two day visits. The last 24 hours of the  
4 visit, 20-point repaglinide insulin and glucose  
5 profiles were determined. The schematic outline of  
6 the slide can be viewed like this. There is a  
7 screening and stabilization phase. The hatched  
8 areas demonstrate the two days that patients were  
9 confined in the hospital every week. During the  
10 second day of which the 24 hour 20-point profiles  
11 were determined. Altogether, the treatment went for  
12 28 days or four weeks and patients treated  
13 themselves in the periods between the hospital  
14 visits.

15 Now, on the next slide the repaglinide  
16 profiles obtained in the study at week four is  
17 depicted. Again, 8:00 in the morning -- the meals  
18 in this trial were given at 8:00, at 1:00, and at  
19 6:00 in the evening. Note here the repaglinide --  
20 again, the rapid absorption with the peak and the  
21 rapid decline to almost baseline levels for all  
22 doses except the four milligram dose. Specifically  
23 note that the nighttime values of repaglinide almost  
24 zero for all patients except some patients in the  
25 high dose.



1 the same plot but for the full dose of four  
2 milligram preprandially to three meals. Repaglinide  
3 concentrations are higher. At this dose, the  
4 increases in insulin secretion as measured in  
5 peripheral blood is more visible with the  
6 enhancement and the decrease down almost to the  
7 placebo group, control group levels, and the very  
8 substantial decreases in blood glucose of an average  
9 80 milligrams per deciliter.

10 On the next slide I'm going to show an  
11 average 24-hour glucoses by dose group as a function  
12 of time. Here's another busy slide. So, the axis  
13 on this slide is time on the X axis, baseline one,  
14 two, three, four weeks treatment, and on the y axis,  
15 the average 24-hour blood glucose. Note first the  
16 placebo group that remains stable throughout the  
17 trial. Then note that we see a dramatic and  
18 significant effect for all doses tested already in  
19 one week. It's also evident that we see the vast  
20 majority of the total effect within the first week  
21 for all doses except the .25 milligram dose. After  
22 three weeks, we hardly see any increased response at  
23 all.

24 On the next slide I'm showing the  
25 classical dose response curve at four weeks which is

1 these data in a different representation as a  
2 function of dose. Placebo level at 240 milligrams  
3 per deciliter on average for 24 hours. We see the  
4 dose response through all the doses tested and the  
5 magnitude of the effect is about 80 milligrams per  
6 deciliter for the four milligram dose.

7           The exposures of repaglinide as measured  
8 AUC repaglinide observed in this study is highly  
9 variable. On this slide is depicted the dose on the  
10 x axis and the AUCs on the y axis. We've plotted  
11 the minimum and the maximum values and the first and  
12 the third quartile with each dose given. Note the  
13 highly variable plasma levels that spans 100-fold  
14 range. Also note, the highest exposures attained  
15 with this expected normal clinical use of three  
16 doses preprandially are of about 830.

17           On the next slide I have repeated this  
18 panel on the left for reference. On the right, I  
19 have plotted the exposures observed in a dose  
20 tolerance trial where patients were dosed all the  
21 way up to 20 milligrams preprandially to four meals.  
22 The line here is, again, the line of the highest  
23 exposures expected in normal clinical use or most  
24 widespread clinical use. We have experience with  
25 exposures of repaglinide ten times higher than that

1 dose all the way up to 11,000. Notably, the  
2 treatment was safe at these doses.

3           We have done special population  
4 investigations comparing 12 young, healthy patients  
5 to 12 elderly, healthy patients. The mean and the  
6 range of the AUC is attained essentially the same,  
7 demonstrating that age as an independent factor does  
8 not influence repaglinide pharmacokinetics. We have  
9 done trials with liver dysfunction comparing 12  
10 healthy subjects to 12 patients with severe liver  
11 disease of Child Pugh Scale B and C -- grade B and C  
12 it's called -- and as expected from the metabolism  
13 and the biliary secretion of the drug, we do see  
14 increases in the exposures observed in these  
15 patients suggesting that careful titration in  
16 patients with liver disease may be warranted.

17           We have also done renal dysfunction  
18 study comparing six healthy subjects to six patients  
19 with mild/moderate disease and six patients with  
20 severe renal disease with creatinine clearances less  
21 than 25. Please note first here that the levels  
22 attained in the normal control group for some reason  
23 turned out lower than we've seen in other trials  
24 with normal controls. Irrespective of that, a  
25 little unexpected thing that happened in this trial,

1 we do see increases in AUC both in the mean and the  
2 range of AUCs with renal dysfunction.

3 I'm going to show you a little more  
4 detail on those things showing the correlation  
5 between the creatinine clearance and the exposures  
6 attained in these patients. So, on this slide on  
7 the x axis, creatinine clearance is depicted and on  
8 the y axis the AUC is repaglinized. The normal  
9 group has high creatinine clearances and low levels  
10 of drug in their blood. The mild/moderate renal  
11 dysfunction have for five out of the six patients  
12 essentially decreased creatinine clearance,  
13 obviously. Essentially, the same levels of  
14 repaglinide with the exception of one outlier.

15 Now, upon scrutiny, this outlier turned  
16 out to have a history of hepatic disease suggesting  
17 that this patient may more fit in the hepatic  
18 impairment group than really, primarily the renal  
19 impairment group. For patients with severe renal  
20 dysfunction with creatinine clearances less than 25,  
21 we do see increases in AUCs, but they're well within  
22 the level or the range of exposures that we're  
23 experienced with and that appears to be safe.

24 We've done drug interaction studies with  
25 free compounds with very a low safety margin with

1 digoxin, warfarin and theophylline. Repaglinide did  
2 not influence any of these three drugs'  
3 pharmacokinetic profile indicating that those  
4 adjustments of these drugs are not necessary when  
5 instituting repaglinide therapy. For warfarin,  
6 we've also looked at the dynamics of warfarin and  
7 there was no effect on the dynamics either. We've  
8 done an interaction trial with cimetidine because of  
9 its inhibition of gastric acid secretion may  
10 interfere with repaglinide absorption. Also because  
11 cimetidine is known to inhibit several liver enzyme  
12 systems. There were no influences of repaglinide on  
13 the repaglinide pharmacokinetic profile.

14           So, before we turn to efficacy, I'd like  
15 to summarize the drug profile so far. We have a new  
16 chemical entity. It's a potent oral insulin  
17 secretagogue with a distinct beta cell binding  
18 profile. It does not induce direct exocytosis of  
19 insulin from beta cells. It does not suppress  
20 protein biosynthesis in beta cells. It's not  
21 neurogenic, photogenic or carcinogenic, and there  
22 are no clinically relevant preclinical safety  
23 findings.                   For the clinical  
24 pharmacology profile, we have a rapid onset with a  
25 Tmax of .7 hours, rapid plasmic clearance. It

1 enhances insulin responses to meals. It results in  
2 clinically significant blood glucose responses. It  
3 is effective in doses from .5 milligrams  
4 preprandially with meals. It is highly variable.  
5 It is excreted by the bile. There are no  
6 significant interactions with either digoxin,  
7 warfarin, theophylline, or cimetidine and no dose  
8 adjustments appears to be required, only for  
9 patients with liver dysfunction. With this, I will  
10 turn to demonstration of efficacy.

11           Efficacy is best demonstrated in three  
12 US trials, placebo controlled US trials, summarized  
13 on this slide. We have titration format trial.  
14 Patients were titrated from .25 to eight milligrams,  
15 or titration range .25 to eight milligrams --  
16 obviously, some patients start below that -- of 18  
17 weeks' duration with 66 patients on repaglinide. As  
18 I just described, we have a dose response trial with  
19 fixed dosing exploring the range .25 to four  
20 milligrams preprandially, four weeks' duration with  
21 120 patients treated with repaglinide. We have the  
22 largest placebo control trial, 65 which explored  
23 doses one and four milligram with three meals of  
24 half a year's duration representing 289 patients on  
25 repaglinide, totalling almost 500 patients on

1 repaglinide in placebo controlled trials.

2           The first trial I'll demonstrate is the  
3 titration format trial, the design of which were  
4 that patients were screened either OHA naive  
5 patients or patients previously treated with oral  
6 hyperglycemic agents. Went through a stabilization  
7 period without any drug, after which they were  
8 randomized to receive either placebo or repaglinide.  
9 They went through a titration period in which they  
10 were titrated through doses .25, .5, one, two, four  
11 and eight milligrams preprandially to three meals.  
12 Patients who did not achieve an increased effect of  
13 eight milligrams over the four milligram dose were  
14 back titrated to four milligrams before the start of  
15 the maintenance phase of the study.

16           At this point, patients were not  
17 titrated further and remained on that determined  
18 optimal dose for the rest of the study. As seen on  
19 the trial, there is good effect of repaglinide and  
20 the placebo groups, glucose controlled, deteriorates  
21 as expected when patients on therapy basically stop  
22 that therapy. It results in a difference between  
23 the two treatments at the end of the study of 1.7  
24 percentage points, HbA<sub>1c</sub>, a very significant and  
25 clinically relevant effect of repaglinide therapy.

1                   I'll repeat the dose response curve to  
2 demonstrate that these results are consistent with  
3 the average BG mean decreases we saw through the  
4 doses tested in the dose response curves of bringing  
5 the blood glucoses from about 240 to 160 on average  
6 for the highest dose.

7                   This slide demonstrates the HbA<sub>1c</sub>  
8 response over time for the largest placebo control  
9 trial with almost 300 patients on repaglinide.  
10 Patients with type 2 diabetes, if they were OHA or  
11 all hypoglycemic agent naive, the requirement was  
12 that their HbA<sub>1c</sub> should be above 6.5. If they had  
13 been previously treated with oral hypoglycemic  
14 agents, the requirement was their HbA<sub>1c</sub> should be  
15 less than 12. Those patients went through a  
16 stabilization phase of two to three weeks' duration  
17 during which they didn't take oral hypoglycemic  
18 agents. They were then randomized to receive either  
19 placebo in the black solid line, or repaglinide one  
20 milligram in the green dashed line, or repaglinide  
21 four milligram in the red dashed line. The  
22 resulting sustained effect on glucose control after  
23 six months or the separation after six months of  
24 therapy here is 1.8 percentage point, HbA<sub>1c</sub>, again  
25 demonstrating the efficacy of repaglinide on glucose

1 control.

2                   On the next slide, I'll show you the  
3 subset of patients in this trial that were naive to  
4 oral hypoglycemic therapy. The placebo group of  
5 naive patients deteriorated somewhat while the  
6 active treatment arms had substantial effects on  
7 glucose control. With separation between the  
8 difference between the placebo, no treatment group  
9 and the four millimeter group was 2.9 percentage  
10 points on average for the patients.

11                   On the next slide, I will show in  
12 absolute numbers where patients in this trial ended  
13 up by dose as a function of HbA<sub>1c</sub>. So, on the x  
14 axis here, we see the HbA<sub>1c</sub> at the end of the trial.  
15 On the y axis, we see the cumulative frequency by  
16 dose group. Note here that if we look at this  
17 point, in the placebo group, half the patients ended  
18 up with HbA<sub>1c</sub>'s above 10. In the one milligram  
19 group, half the patients ended up with HbA<sub>1c</sub>'s less  
20 than 8.3. In the four milligram group, half the  
21 patients ended up with glucose control of HbA<sub>1c</sub> less  
22 than 7.8.

23                   We saw in fasting morning plasma  
24 glucoses were consistent with these data with  
25 somewhat deterioration in the placebo group -- I'm

1 now back to talking about all patients, I should say  
2 -- somewhat deterioration in placebo group of 20  
3 milligrams per deciliter. The effect on the axle  
4 arms of the study are a decrease of 50 milligrams  
5 per deciliter in fasting morning plasma glucose.

6 To study safety, one-year comparator  
7 trials were done. I'll just go through the trial  
8 design of these safety studies in some detail.  
9 Patients were either naive or previously treated  
10 with oral hypoglycemic agents. They were screened  
11 and went directly from their therapy if they had one  
12 before into either repaglinide or the comparator.  
13 This particular trial I've shown you is the US trial  
14 in which glyburide was used as a comparator.

15 Patients then went through a titration  
16 to fixed glucose control, meaning that we basically  
17 titrated the drugs to equivalent glucose control.  
18 When the beginning of the maintenance phase of 12th  
19 month began no dose adjustments were possible should  
20 glucose control deteriorate at that point. So,  
21 importantly, they were titrated to fixed targets,  
22 titrated to equivalence, and then the dose was  
23 maintained. The results of this study was, as  
24 expected from the design, that we see equivalent  
25 responses in HbA<sub>1c</sub> over time between repaglinide and

1 the comparator. Repaglinide is the solid line and  
2 that should have interest.

3 On the next slide is shown a summary of  
4 the glucose response data in all those five  
5 comparator trials. As shown here on the y axis is  
6 difference between repaglinide and the comparator in  
7 the change from baseline over time. Now that means  
8 that if we have a negative number here, it means  
9 that it is in favor of repaglinide and a positive  
10 number is in favor of the comparator. Just to  
11 summarize again, the 49 trial, as I just showed you  
12 on the previous slide, has a confidence interval  
13 that symmetrically around zero demonstrating the  
14 equivalent effect in this particular trial design on  
15 glucose control. We also obtained equivalents in  
16 other trials and one of the trials, the glipizide  
17 comparison, turned out in favor of repaglinide in  
18 terms of glucose control.

19 The efficacy of repaglinide was  
20 confirmed in a combination study with metformin. In  
21 this trial, metformin monotherapy failures  
22 inadequately treated with metformin were randomized  
23 to either receive repaglinide as monotherapy,  
24 metformin as monotherapy, or the combination between  
25 the two drugs. Patients went through a titration

1 period and then were on fixed dosing for three  
2 months thereafter. The effects on blood glucose  
3 control as measured by HbA<sub>1c</sub> is depicted on the next  
4 slide, showing as expected that in these metformin  
5 therapy failures, the metformin monotherapy remained  
6 essentially constant as does repaglinide  
7 monotherapy. But in the combination arm of the  
8 study, there are very substantial decreases from 8.7  
9 down to 6.9 in glucose control demonstrating  
10 synergistic effect of the two compounds.

11 Note the end result here: the average  
12 glucose control less than seven and more than half  
13 the patients -- and that's not shown on this slide -  
14 - had glucose less than seven at this point.  
15 Essentially, those metformin failures were rescued  
16 by the add-on of repaglinide therapy.

17 So, in summary, the clinical  
18 pharmacology profile of repaglinide is as follows:  
19 rapid onset Tmax within an hour; rapid plasma  
20 clearance; enhances insulin responses to meals.  
21 Repaglinide results in clinically significant  
22 glucose responses. It's effective from .5  
23 milligrams. It's highly variable. It is excreted  
24 by the bile. There are no significant drug  
25 interactions with either digoxin, warfarin,

1 theophylline, or cimetidine. Dose adjustments seem  
2 to be required only for liver dysfunction patients.

3           The summary of the efficacy profile --  
4 turn the discussion over to safety, the vast  
5 majority of the response within one week, 40 to 80  
6 milligrams per deciliter on average. Those response  
7 through the doses .5 to four milligrams  
8 preprandially with three meals. Significant  
9 difference versus placebo repeated in both titration  
10 and fixed dose formats. Very consistent results  
11 with overall same effects on blood glucose. It  
12 improves blood glucose, depending on the trial and  
13 the subset, anywhere from 1.6 to 1.9 HbA<sub>1c</sub> on  
14 average. There's a maintenance of glycemic control  
15 for at least one year and there's a substantial  
16 additive effect to metformin in the trial where the  
17 metformin failures were actually rescued back into  
18 good glucose control with repaglinide.

19           With this, I'd like to turn over the  
20 presentation to Dr. Edwards who will present safety  
21 of the compound.

22           ACTING CHAIRMAN SHERWIN: I'm sorry.  
23 Dr. Cara would like to ask a couple of questions. I  
24 had hoped that we would go through, but that's okay.

25           DR. CARA: Just while it's still fresh

1 on my mind, a couple of questions.

2 Do you know whether the binding sites  
3 for the repaglinide actually get down-regulated?  
4 Does that have any clinical significance in terms of  
5 development of tolerance?

6 DR. STRANGE: Whether repaglinide  
7 receptors get down-regulated?

8 DR. CARA: Binding sites.

9 DR. STRANGE: I'm not the right person  
10 to answer that question.

11 Dr. Carr, do you have an opinion about  
12 this?

13 DR. CARR: Yes, my name is Richard Carr.  
14 I work in research at -- of Copenhagen. We  
15 conducted experiments in vivo over three weeks and  
16 we see no evidence of down-regulation of these  
17 receptors.

18 DR. CARA: Does that mean then that  
19 there's no evidence of tolerance to the doses that  
20 you're talking about?

21 DR. STRANGE: The best clinical evidence  
22 we have of tolerance or no tolerance is the yearlong  
23 trials where we've seen sustained effect --

24 DR. CARA: Sustained, good.

25 DR. STRANGE: -- for a year. We do see,

1 as is seen in I think all diabetes trials, that  
2 there is a little decrease in the beginning,  
3 probably as a function of participating in the  
4 trial. We do see that and then a little rebound.  
5 But we do see sustained effect. In the naive  
6 subsets in the yearlong trials, we do see a  
7 sustained effect of a decrease of HbA<sub>1c</sub> of more than  
8 one or maintained for more than the 14 months of  
9 trial duration.

10 DR. CARA: You show that there's quite a  
11 bit of variation despite equal dosing. You show  
12 that there's quite a bit of variation in terms of  
13 plasma levels of repaglinide. Even though you  
14 showed mean data for each dose group, do you have  
15 any evidence showing that the doses of repaglinide  
16 or the plasma levels, if you will, correlate with  
17 blood sugar control on an individual patient basis?

18 DR. STRANGE: If you look at the whole  
19 64 trial, there is a correlation between the  
20 attained levels in plasma and the blood glucose  
21 control but there is variability. So, the  
22 prediction for any given patient is not very good.  
23 But I mean, there is the exposure response through  
24 all the exposures that we have tested. But because  
25 of the scatter, the prediction for any given patient

1 is not very good. I mean, it's tough to predict  
2 from the onset.

3 Page 23 of the briefing document. I  
4 don't have that right here. That's right. We put a  
5 figure of that in the briefing document at page 23.  
6 There it is. Dr. Sherwin has it now.

7 What you see in this figure is the  
8 repaglinide exposures observed following doses of  
9 repaglinide. If you have very, very good eyes, you  
10 can actually see that each of the doses has a symbol  
11 on here. Also shown is the regression line showing  
12 that in this regression which is basically a model,  
13 the decrease in average blood glucose as a function  
14 of exposure. So, with one decade here, we see  
15 roughly, in the model data, a decrease of average  
16 blood glucose of 40 milligrams per deciliter.

17 But to answer your question, because of  
18 the scatter, the prediction for any given patient at  
19 the onset is not very good.

20 ACTING CHAIRMAN SHERWIN: Is that  
21 related to binding proteins?

22 DR. STRANGE: Could you repeat that  
23 question? Sorry.

24 ACTING CHAIRMAN SHERWIN: I was just  
25 curious. I don't want to belabor -- binding

1 proteins. Obviously, the drug is tightly bound to  
2 protein. Does the amount or affinity of the drug to  
3 binding proteins account for the variable responses?

4 DR. STRANGE: The drug is found with 98  
5 percent of plasma protein, the vast majority of  
6 which is albumen. That correlation has not been  
7 made but it's very highly unlikely because of the  
8 very high protein binding. The free drug available  
9 will be relatively independent of the absolute  
10 protein level because of the very, very high protein  
11 binding, percent of protein binding.

12 DR. FOSSLER: Hi. Mike Fossler, FDA.

13 This is probably expected for a drug  
14 that's metabolized by 3A4. There's a lot of free A4  
15 in the gut and so you're going to see day-to-day  
16 fairly wide fluctuations in bioavailability. That's  
17 probably the most likely explanation.

18 ACTING CHAIRMAN SHERWIN: Thank you.

19 DR. CARA: Yes, but when I look at this  
20 graph on page 23 in looking at the data, I mean,  
21 you're looking at a graph that is really comparing  
22 log area under the curve versus change in blood  
23 glucose. It strikes me that it's awfully flat.

24 DR. STRANGE: Well, I mean, if you look  
25 at the y axis -- can you turn that back on? If you

1 look at the y axis on that specific plot, you'll see  
2 that this difference here is 100 milligrams per  
3 deciliter in average blood glucose. Now, that's a  
4 very, very big difference, 100 milligrams in average  
5 blood glucose. I mean, if you have one patient who  
6 is on average, let's say, 230 which is pro-control  
7 and you bring that patient with 100 here down to 130  
8 or 140 or 150, that's a decent control, very decent  
9 control. So, I mean, this curve is a little  
10 deceptive. It understates the effect of the drug.

11 DR. MOLITCH: That's not the point. The  
12 point is that you have such wide variations in the  
13 area under the curve with such a little change in  
14 blood glucose. You've got 100-fold change in  
15 concentration for a relatively small change. Also,  
16 even for the same very large amounts, you have such  
17 a wide change in bioactivity for even very huge  
18 amounts of drug.

19 What's the explanation for the lack of  
20 the dose response, essentially?

21 DR. STRANGE: The lack of dose response  
22 --

23 DR. MOLITCH: Or the minimal dose  
24 response.

25 DR. STRANGE: There is a dose response.

1 Let's state that first. Then we'll say the  
2 explanation for the variation is that it is probably  
3 the state of the patients when the patient is  
4 treated that's more important than the absolute. I  
5 mean, it's the responsivity of the patients. The  
6 patients ability to respond, their sensitivity to  
7 this therapy that's more.

8 I'd like to call in one other point that  
9 seems to be a little disturbing here. What you see  
10 here is intersubject variability, right? You see  
11 one patient, to the next patient, to the next  
12 patient which, admittedly, there is a large  
13 variability. For the intraindividual variability,  
14 when you measure the exposures attained at week one,  
15 two, three, four in this trial, that is very  
16 substantially smaller. I think the intersubject  
17 variability is 95 percent while the intersubject  
18 variability is 35 percent.

19 So, the prediction you have in any given  
20 patient you treat over time is going to be the same.  
21 You don't have this large variability once you treat  
22 one patient.

23 DR. MOLITCH: I mean, are we dealing  
24 with a salability type of phenomena to binding site  
25 for this drug so that everything that everything

1 that's in excess really isn't doing very much? I  
2 mean, are we really having a variability of effect  
3 at the cellular level?

4 DR. STRANGE: That would be pure  
5 speculation so I'd rather not venture into that.

6 DR. CARA: Do you have data on  
7 individual patients that have been treated with  
8 progressively higher dosages to see if there is, in  
9 fact, a dose response on an individual basis?

10 DR. STRANGE: There has been done dose  
11 escalation trials in individual patients in which  
12 patients have been receiving -- it was before we  
13 really got the dose range nailed down, but they  
14 received first, a half milligram, then two  
15 milligrams, and eight milligrams. We do see  
16 increased response in the same patients with the  
17 higher dose. Yes, that is we do see increased  
18 response.

19 DR. CARA: Is it as shallow as this?  
20 How does it compare to the data that you've got up  
21 here?

22 DR. STRANGE: This is a very long time  
23 ago so I'd rather not answer that straight.

24 Yes?

25 DR. HIRSCH: Just to understand this

1 curve, what is the ordinant? It says mean glucose  
2 over -- what's measured?

3 DR. STRANGE: Yes, I'm sorry about that.  
4 BG mean is the average 24 hour glucose. What has  
5 been done is that you've taken the AUC of the  
6 glucose over the 24 hour period and divided by the  
7 time which is essentially 24 hours. So, I mean, if  
8 you took the response over time and then you made it  
9 one flat line, what is the average?

10 DR. HIRSCH: So, food intake variability  
11 could be a big factor in this as well, which must  
12 vary enormously in these people, or not?

13 DR. STRANGE: No.

14 DR. CARA: But even so, you're talking  
15 about a blood glucose change of maybe 50 for a dose  
16 that varies by 1,000-fold.

17 DR. HIRSCH: I understand.

18 What happens, by the way, when the drug  
19 is given and they don't eat anything? Someone must  
20 get sick sometime or something, whatever.

21 DR. STRANGE: We've done a large amount  
22 of healthy volunteer studies that have been done  
23 fasting and I think the very first curve -- not I  
24 think. The very first curve I showed you was done  
25 fasting. Healthy individuals have no problems.

1 Some of them experienced hypoglycemia, not  
2 unexpectedly, but otherwise, we don't see any --

3 DR. HIRSCH: The diabetic subjects? Has  
4 that been studied in them as well?

5 DR. STRANGE: I don't think we've ever  
6 given this drug fasting to diabetes patients. I get  
7 confirmatory nods. No, we haven't done that.

8 DR. KREISBERG: Robert?

9 ACTING CHAIRMAN SHERWIN: Okay.

10 DR. KREISBERG: Can I ask, are we going  
11 to revisit this particular issue?

12 ACTING CHAIRMAN SHERWIN: We're going to  
13 go back and go over everything. This is just the  
14 beginning.

15 My view would be let's let the company  
16 finish their presentation. We'll take a break and  
17 then we'll begin the real questioning.

18 DR. EDWARDS: Okay, good morning, ladies  
19 and gentlemen. You heard earlier from Dr. Reno our  
20 encouraging preclinical safety profile. I'd like to  
21 continue now by describing the clinical safety  
22 features of repaglinide.

23 Let's start by looking at the duration  
24 of exposure in the control trials. This data shows  
25 you here the number of subjects exposed to

1 repaglinide versus the time intervals of their  
2 exposure. Let me draw your attention to this column  
3 which indicates that we had 831 patients treated for  
4 more than a year with repaglinide. The total  
5 exposure exceeds 1,000 patient years of repaglinide  
6 which we think is fairly substantial for this stage  
7 in the drug's development.

8 Now, Poul Strange made some observations  
9 specific to the study 049 which is the US trial of  
10 this type. Just let me extend those observations.  
11 Most of the safety exposure comes from a long-term  
12 active control trials including all those 831  
13 patients, as you saw. So, just let me try and  
14 orientate you to the type of patients that we are  
15 talking about here.

16 These trials, the basic design of which  
17 Dr. Strange explained, you can see there's a full  
18 year treatment with repaglinide after the titration  
19 phase. To get you a feel for the type of patients,  
20 if we cull all our data across the -- trial that  
21 I'll describe to you, the typical patient was 60  
22 years old. They had had their diabetes about eight  
23 years and had an HbA<sub>1c</sub> of just under eight, although  
24 that describes an enormous variation in that  
25 variable.

1                   Let's take a look now at the comparator  
2 trials. This is the trial 049 that Dr. Strange  
3 showed you with 576 patients. There were two other  
4 trials of this type, 046 and 050, where glyburide  
5 was the comparator agent. There was one trial 048  
6 where the comparator agent was glipizide, showing 81  
7 patients exposed and one trial 047 in which  
8 glipizide was the comparator agent. I want to draw  
9 your attention to the fact that all of the trials  
10 featured a two to one randomization of repaglinide  
11 versus comparator agent.

12                   This slide summarizes for you the  
13 exposure by age, by gender and by race with the US  
14 studies on the left of the slide as you look and the  
15 European studies on the right. If we look across  
16 the age line, we can see that approximately 25  
17 percent of patients in this population were above 65  
18 years of age. One-third were women and within the  
19 United States' trials, there was a reasonable racial  
20 mix of the expected population, while in Europe  
21 almost all the patients were Caucasian.

22                   This slide deals with discontinuations.  
23 On the left-hand side, you see the placebo  
24 controlled trials. Those trials were the focus of  
25 Dr. Strange's presentation. On the right-hand side,

1 you see the one-year comparator trials which I will  
2 be focusing on. At the top of the slide, you can  
3 see the number of patients exposed. If we go down  
4 to the proportion completing, you will see that more  
5 patients on repaglinide than placebo actually  
6 completed the trial period. Now, the main reason  
7 for this difference is seen here which is the large  
8 number of placebo patients were withdrawing because  
9 of hypoglycemia ineffective therapy. However, if we  
10 look at the adverse event line, we can still see  
11 that placebo patients actually suffered more AEs  
12 than the repaglinide.

13 Now, if we look at the right-hand panel  
14 in the slide where we look at repaglinide versus all  
15 the comparator agents culled, you can see that the  
16 proportions completing repaglinide and comparator  
17 agents were the same. The discontinuation rates for  
18 adverse events were the same. I'd like to draw your  
19 attention to this line here which we'll return to  
20 later which is that twice as many patients in the  
21 comparators withdrew with hypoglycemia than with  
22 repaglinide.

23 On this slide, we're looking at adverse  
24 events overall. For an event -- here to appear on  
25 the slide, it had to be experienced by five percent

1 more patients in any one treatment category. Now,  
2 if we look first at the repaglinide versus placebo  
3 and just look down those two lines, the only thing  
4 that seemed to stand out was this here, something in  
5 the respiratory area. But when we look across the  
6 repaglinide versus active comparison trials, we  
7 really don't see any difference. So, we think that  
8 the safety profile is good and it's very comparable  
9 to active comparitors tested.

10 Now, we looked for evidence of dose  
11 response in our adverse events and really didn't see  
12 anything. I just want to revert for a minute to  
13 this trial, trial 036, described earlier by Dr.  
14 Strange, which was the ascending tolerance trial in  
15 type 2 diabetics. To get you orientated here, this  
16 was a dose escalation trial starting at 16  
17 milligrams per day and going up to 80 milligrams a  
18 day. That is five times the maximum recommended  
19 dose. You can see there were very few adverse  
20 events reported in 15 patients on repaglinide and  
21 five on placebo. I'd like to point out at this  
22 point that we didn't detect any changes in liver  
23 enzymes of note, nor any changes in ECG intervals,  
24 or indeed, any evidence of ischemia.

25 I'd like now to turn to hypoglycemic

1 events in one-year trials. Just let me explain the  
2 nomenclature on the slide for you. The top line is  
3 the number of patients exposed which are the numbers  
4 we've seen before. The next line is the number of  
5 patients who experienced one or more hypoglycemic  
6 events. The next line is the percentage of patients  
7 who d/c discontinued because of hypoglycemia. The  
8 next line is the percentage of patients who had a  
9 hypoglycemic episode where blood glucose was  
10 measured. So, in this case, 50 percent of the  
11 episodes reported there was actually a blood glucose  
12 measurement made. The next line is the percentage  
13 of patients who had a blood glucose when it was  
14 measured which was less than the threshold value of  
15 45 milligrams per deciliter. Finally, the mean  
16 blood glucose measured in this population of  
17 patients.

18 Now, if we start at this line and we  
19 look across, we can see that the overall frequency  
20 of hypoglycemia appears very comparable. However,  
21 this difference, apparent small difference, between  
22 glyburide and repaglinide in repaglinide's favor, it  
23 becomes more apparent when you look down the slide.  
24 If we look at the proportions discontinuing, you can  
25 see it was lowest in repaglinide. If we look at

1 those patients who had a blood glucose value less  
2 than four to five, it was half the number of  
3 patients with repaglinide than with glyburide. So,  
4 we find that information on hypoglycemia very  
5 encouraging and we'd like to return to that later in  
6 our presentation in discussion section.

7 I'd now like to turn to cardiovascular  
8 events and start with a simple slide. These are the  
9 numbers we've seen before. The number of patients  
10 in the one-year, long-term active comparator trials  
11 1,228 with Prandin, repaglinide, 417 with glyburide,  
12 and 81 with glipizide. This slide shows you the  
13 crude event rates and the percentage of patients  
14 experiencing those events for three types of events:  
15 serious cardiovascular events, cardiac ischemic  
16 events, and death due to cardiovascular events.

17 If you look across the serious  
18 cardiovascular event line first, you see four  
19 percent of patients had such events with  
20 repaglinide, two percent with glyburide and six  
21 percent with glipizide. The cardiac ischemic  
22 events, anginas, in total myocardial infarctions and  
23 so on in two percent of repaglinide patients, one  
24 percent of glyburide patients, and five percent  
25 glipizide patients. If we look at death due to any

1 cardiovascular event, in this case, within  
2 capillaries 10/10 and 10/40 of the ARD system, we  
3 see there were six such deaths now returned with  
4 repaglinide and two deaths with glyburide. Please  
5 bear in mind when you look at these numbers, you  
6 need to look at the relative exposure rates.

7           These were the deaths. You can see here  
8 the treatment years for repaglinide, as I said about  
9 1,000, and this shows you the data for all the  
10 comparitors pulled. We're five infarcts with  
11 repaglinide while with one comparitor, one death due  
12 to cardiac failure with repaglinide. One heart  
13 block, as it is recorded, with a comparitor agent  
14 and one event reported as a cardiac arrest meaning a  
15 total of six versus a total of three such events.

16           Now, we're going to look at the data  
17 that we have on cardiovascular events in a somewhat  
18 more sophisticated way. This slide shows you  
19 cardiovascular serious adverse events. I have three  
20 thoughts of this type, so just let me explain the  
21 first one carefully. What is shown here is the time  
22 to first event with each little blip in the line  
23 representing the event. The exposure time in these  
24 long-term -- trials here and the cumulative  
25 incidence of such events on the y axis.

1           The solid blue line here represents the  
2           repaglinide values. The fainter blue lines at each  
3           side, the 95 percent confidence intervals for these  
4           events. The light underneath shows you the value  
5           for all the comparitors pulled with their confidence  
6           intervals. As you can see, while in the absolute  
7           numbers the repaglinide are larger, that the  
8           confidence intervals clearly overlap.

9           Now, we can cut this data in many  
10          different ways, and indeed, we have cut it in many  
11          different ways. What this shows you is the  
12          cumulative instance unadjusted for the same events  
13          seen on the previous slide. Now, the data is  
14          difficult to interpret for a couple of reasons.  
15          Firstly, let's deal with the placebo. As Dr.  
16          Strange showed you, we had asymmetric randomizations  
17          with placebo. So that in placebo control trials,  
18          far more patients were actually treated with active  
19          agent than placebo. As I showed you earlier, a lot  
20          of the patients withdrew because of ineffective  
21          therapy.

22          With glipizide, while the percentage of  
23          patients with events was high, the absolute number  
24          of events is small. You can see if we just look at  
25          it in a simple way, repaglinide here appears in the

1 middle between glipizide, gliclizide and glyburide  
2 shown here. Now, on the same data set if we look at  
3 all acute ischemic cardiovascular events -- so this  
4 would include myocardial infarctions and all anginal  
5 episodes. What you can see here is essentially the  
6 same pattern with glipizide sticking out up here,  
7 but now the data for repaglinide, glyburide,  
8 gliclizide appears much closer together.

9                   Now, in a Cox Regression model which has  
10 looked at this data, we see some fairly  
11 straightforward things which we would expect, I  
12 think, which gives us some confidence in the model.  
13 Firstly, if we look at cardiovascular events  
14 overall, as one would expect, the older was the  
15 patient, the greater was the risk a year. The same  
16 was true with patients who had a previous medical  
17 history of cardiovascular risk. This, I think, is  
18 somewhat important in the sense that when you  
19 analyze the baseline covariates in some of the  
20 trials that the patients are not equally distributed  
21 for previous history of cardiovascular risk. I  
22 would like to return to that later. Also, as you  
23 would expect, patients with very baseline ECG  
24 abnormalities also had a high risk. And if we look  
25 from the time of the subject's first hypoglycemic

1 event, it's also to some extent an important  
2 covariate in determining the time at first event in  
3 the model.

4           So, I've shown you some absolute numbers  
5 and I've shown you some cumulative incident plots.  
6 I now want to just return briefly to this famous  
7 landmark study, the UGDP. Many people here, I'm  
8 sure are very familiar with this trial. It has been  
9 very significant in determining labeling of oral  
10 hypoglycemic agents for a long time -- first off in  
11 1961 and the results are still with us. What you  
12 can see here is the cumulative mortality rate in  
13 percentage versus the years in the trial. To remind  
14 those of you who are unfamiliar, the chart is best  
15 known for having shown the success risk of  
16 cardiovascular events with tolbutamide versus the  
17 other groups tested insulin here or placebo.

18           Now, notice the duration of the trial.  
19 If we had looked at this trial data in a shorter  
20 period of time, we might not have drawn the same  
21 conclusion. Because if we just look at the first  
22 couple of years, the actual event rates were higher  
23 with insulin than with either tolbutamide or  
24 placebo. Just to put this in context and clear that  
25 the data is not drawn contemporaneously. What we've

1 just shown here to put this in perspective is the  
2 actual event rates that we're talking about, this is  
3 repaglinide, this is glubanclumide and of course if  
4 I put glipizide on it, it would have been up here.  
5 You can see that the actual event rates for  
6 cardiovascular mortality are low. You also need to  
7 bear in mind that with UGDP we were talking about  
8 patients within one year of diagnosis. The average  
9 patient in the trials we're talking about has had  
10 their type 2 diabetes eight years.

11 As I try and summarize the safety  
12 profile, overall mortality versus comparator agents  
13 when we look at them together is the same. That is  
14 true whatever we look at, whether we look at  
15 malignancies, whether we look at cardiovascular  
16 disease. When we look at the overall safety profile  
17 -- and here, I'm thinking of the slide where I  
18 showed you all events with a frequency of more than  
19 five percent -- the profile appeared very comparable  
20 to approved OHAs. We believe the high -- profile is  
21 acceptable and maybe good. We feel very encouraged  
22 about that area with repaglinide.

23 I've shown you the overall  
24 cardiovascular profile is comparable to  
25 sulfonylureas. When we look at our data in

1 isolation in comparison with glyburide, we do see a  
2 small increase in non-fatal cardiovascular events.  
3 We believe other than as Dr. Strange told you, that  
4 in patients with liver impairment -- other than  
5 those patients, we do not believe special  
6 precautions are required regarding dose adjustment.  
7 We think that we have really quite a wide  
8 therapeutic index. If you think about the 036 trial  
9 where I mentioned that patients had received up to  
10 80 milligrams a day, the average area of the cadre  
11 you see there was on the order of 5,000 nanograms  
12 per mil per hour. Dr. Strange told you that he  
13 expected the upper limit in patients within the  
14 therapeutic range recommended was about 800. As you  
15 recall, we saw very few events in that trial.

16 To try and summarize our formal  
17 presentation for you, if we look at the preclinical  
18 profile, repaglinide, a new chemical entity, benzoic  
19 acid derivative -- an oral insulin secretagogue with  
20 distinct beta cell binding sites. Insulin is not  
21 released by direct exocytosis. The compound is not  
22 mutagenic, teratogenic or carcinogenic and we saw no  
23 clinically relevant preclinical safety changes.

24 The pharmacology is a rapid onset of  
25 action. The T<sub>max</sub> of .7 hours and rapid plasma

1 clearance. We saw it enhanced insulin response to  
2 meals, a clinically important blood glucose  
3 response. The drug was potent, effective in doses  
4 of five milligrams and above. We saw a wide  
5 variation AUC repaglinide, which has already been  
6 briefly discussed. Excretion more than 90 percent  
7 by the bile. We saw informal drug interaction  
8 studies. No effective repaglinide on the  
9 pharmacokinetics, digoxin, warfarin, theophylline  
10 and no effect on cimetidine of the kind that exhibit  
11 -- We feel that dose adjustment will only be  
12 required specifically for patients with liver  
13 dysfunction where careful titration is advised.

14 In the efficacy profile, we saw a prompt  
15 blood glucose response within one week of therapy.  
16 We saw in 064 a dose response in the range of .5 to  
17 four milligrams given preprandially three times a  
18 day. In both titration 033 and fixed dose 044, 064  
19 and 065 studies, we saw a significant benefit to  
20 repaglinide versus placebo. We've absolute  
21 reductions depending on the study between 1.6 and  
22 2.9 percentage points in HbA<sub>1c</sub>. We saw that in the  
23 long-term study, glycemic control was maintained as  
24 well as with comparator to agents, and we saw a  
25 substantial additional effect when repaglinide was

1 added to metformin failures.

2 Dr. Sherwin, Dr. Fleming, that concludes  
3 Novo Nordisk's formal presentation.

4 ACTING CHAIRMAN SHERWIN: Thank you.

5 I would like to thank Novo Nordisk for a  
6 succinct presentation. It was really one of the  
7 first times we were really on schedule. I really  
8 appreciate that.

9 What I'd like to do is take advantage of  
10 the break time now and give people a chance to sort  
11 of digest the presentation. My watch says 12  
12 minutes to 10:00. I would suggest that we begin at  
13 five after 10:00.

14 (Whereupon, off the record at 9:48 a.m.,  
15 until 10:13 a.m.)

16 ACTING CHAIRMAN SHERWIN: Okay.

17 Hopefully, we can reconvene.

18 We've conferred about, you know, how to  
19 proceed. My feeling is that the best way to proceed  
20 at this point is to open up the forum to the  
21 Committee and have them ask general questions that  
22 have arisen as a result of the presentation. Then  
23 we'll get to the discussion of the specific  
24 questions that are raised by Dr. Fleming.

25 So, I'd like to open it up to the panel.

1 I know Dr. Kreisberg had some questions.

2 DR. KREISBERG: I defer to Dr. Marcus.

3 ACTING CHAIRMAN SHERWIN: Oh, Dr. Marcus  
4 has more burning questions? Okay.

5 DR. MARCUS: I have one large question,  
6 but a couple of very small ones that perhaps you  
7 could just address first.

8 Is this drug approved elsewhere -- that  
9 is, other countries -- and in particular, is there  
10 any evidence from any work you may have done in Asia  
11 which might give some insights as to how Asian-  
12 Americans might respond? Your representation by the  
13 Asian community is extremely small that you  
14 presented.

15 DR. EDWARDS: Martin Edwards. I think I  
16 can address that for you.

17 The current situation in Japan is we do  
18 have clinical trial programs active in Japan. We  
19 are currently in phase III in Japan and we have  
20 approximately a couple of hundred patients treated  
21 with repaglinide. So, that's the actual situation.  
22 We haven't seen anything untoward in terms of  
23 safety. It looks like the patients will probably  
24 have somewhat lower doses in Japan. That's not  
25 unusual.

1 DR. MARCUS: Okay, thank you.

2 So, because this drug leads to some  
3 interaction with calcium channels, I just wonder  
4 among drug interactions, is there any interaction  
5 that you've seen with people taking calcium channel  
6 blockers?

7 DR. EDWARDS: The simple answer is no.

8 DR. MARCUS: Okay, good.

9 Now, my major concern has to do with an  
10 area that has really been very little discussed in  
11 your submitted documents and that has to do with  
12 weight loss. I think we all know that any  
13 intervention involved with management of patients  
14 with type 2 diabetes, whether it be an exercise in  
15 nutritional or a pharmacological intervention, is  
16 highly interactive with any changes in body weight.  
17 I'd like to know whether there were on average any  
18 changes in weight during your studies? And whether  
19 there's any relationship even if there were no  
20 change in the average weight between change of  
21 weight of an individual person and the response to a  
22 drug?

23 Also, in line with that, there's the  
24 whole panoply of other cardiovascular risk factors  
25 which are certainly paramount to patients with

1 diabetes. Triglycerides, high density lipoprotein,  
2 low density lipoprotein, cholesterols, fibrinogen,  
3 plasminogen activator inhibitor, and lipoprotein a,  
4 and there was really vanishingly little of that in  
5 your formal documents and nothing of that in your  
6 presentation. I would ask that somebody address  
7 those.

8 DR. WHISNANT: Thanks for the  
9 opportunity to comment. All of those are important  
10 questions and we're happy to respond. I'm trying to  
11 find you a slide on the weight changes.

12 Let me summarize briefly by saying that  
13 in the one-year comparator trials, that the patients  
14 on average experienced virtually nil change in  
15 weight, but that's an average phenomenon. That is,  
16 patients on repaglinide in a table that I will show  
17 you and a figure I'll show you lost about .6 kilos  
18 over the one-year period of time. It's different  
19 for patients who were completers versus patients who  
20 dropped out of the trial early-on. That compares  
21 to, for various trials, somewhere between .6 and one  
22 kilos of weight gain on average for the comparator  
23 drugs.

24 The slide in front of you summarizes  
25 weight change for all patients in the US comparator

1 trial, 049. Note the distribution of patients  
2 within five percent and below nil change, and within  
3 five percent above a nil change. Notice that for  
4 repaglinide in the gray bars or pale blue bars, that  
5 there is a slightly higher columns minus for the  
6 less than five percent and for the zero to five  
7 percent below the mean compared to glyburide. The  
8 other trials look about the same.

9           The second part of your question is do,  
10 for instance, highly responsive patients or naive  
11 patients gain more weight during their response to  
12 repaglinide as is very often seen with other OHA  
13 drugs? The answer is basically yes. We find that  
14 the distribution of patients -- it's all right. I  
15 think the point is well made. The distribution of  
16 patients for naive patients in the 49 trial is  
17 somewhat above no change at the end of the year,  
18 with most of those being between zero and five  
19 percent weight gain and some 25, a quarter of the  
20 patients would gain even more than that. The  
21 variability of weight change for some patients is  
22 very significant, either very significantly lost or  
23 very significantly gained.

24           DR. MARCUS: Was an attempt rate made to  
25 control dietary intake? What sort of dietary advice

1 was given to these patients during the course of the  
2 trial?

3 DR. WHISNANT: Patients who entered the  
4 comparator trials were given standard dietary, if  
5 you will, advice during the run-in period of the  
6 trial, but there was no long-term, for instance,  
7 intensified program like is being planned for the  
8 DPP trial or for other long-term intensive  
9 management kinds of trials. These were conventional  
10 diabetes care trials with the addition of  
11 repaglinide versus comparator.

12 DR. MARCUS: And the other  
13 cardiovascular risk factors?

14 DR. WHISNANT: The other cardiovascular  
15 risk factors actually, in response to a question  
16 that we're going to address in a little bit about  
17 cardiovascular risk itself as an outcome, I can tell  
18 you that there was an imbalance in the 49 trial of  
19 patients who had had prior MIs, angina, baseline EKG  
20 changes, et cetera, and I'll show you that slide in  
21 a little while.

22 The other cardiovascular risk factors  
23 that you asked about and it's, in effect, the  
24 population risk factors, I'd like to ask Dr. Edwards  
25 to address lipid changes, et cetera.

1 DR. EDWARDS: Thank you.

2 I think the most straightforward answer  
3 I can give is that we did not see changes in the  
4 lipids in our long-term one-year trials. We did  
5 look, as I briefly mentioned about important  
6 covariates, our focus was to look for baseline  
7 imbalances between the groups in the long-term  
8 trials. With respect to lipids, there were no  
9 imbalances.

10 ACTING CHAIRMAN SHERWIN: Are there  
11 other data that we could see?

12 DR. EDWARDS: On lipids? We have not  
13 prepared slides on lipids. We can. We have got our  
14 integrated summary of efficacy with us. If you  
15 would like, we could prepare a couple of slides --

16 ACTING CHAIRMAN SHERWIN: Well, you  
17 know, depending on what you can do, perhaps after  
18 the lunch break --

19 DR. EDWARDS: Yes.

20 ACTING CHAIRMAN SHERWIN: -- whatever  
21 data you might have on cardiovascular risk factors  
22 would be helpful.

23 DR. KREISBERG: I didn't understand his  
24 response, Bob.

25 Are you saying that there was no

1 difference in cardiovascular risk factors such as  
2 lipid levels when you evaluated your drug versus the  
3 comparator? Is that what you're saying?

4 DR. EDWARDS: Yes.

5 DR. KREISBERG: But there must have been  
6 changes in lipids that occurred as a consequence of  
7 the use of the drug compared to placebo, or is that  
8 not true?

9 DR. EDWARDS: Yes. Well, what I was  
10 focusing on, I was thinking of cardiovascular risks  
11 in terms of our long-term active comparator trials  
12 because that is where most of the exposure is. The  
13 answer I gave was that if we look at the change in  
14 lipids in those trials, we don't see any difference  
15 between our drugs and the comparators we tested.

16 When we looked to the baseline  
17 imbalances at randomization in terms of risk  
18 programs, we saw some important differences. We saw  
19 some important differences with respect to previous  
20 cardiovascular history, with respect to ECG  
21 differences, but we did not see differences in  
22 respect to lipids at baseline.

23 DR. KREISBERG: But there must have been  
24 some --

25 I'm sorry, go ahead, Bob.

1 DR. MARCUS: No, my question was -- I  
2 mean, it was simply, if you did a repeated measures  
3 analysis of variance on any one of these  
4 lipoproteins or other biochemical risk factors, was  
5 there a difference across time in response to your  
6 drug?

7 DR. EDWARDS: No, we don't believe so.  
8 We'll check in the ISE for you. We don't believe  
9 that's the case.

10 DR. MOLITCH: We all want that  
11 information.

12 DR. EDWARDS: Okay.

13 ACTING CHAIRMAN SHERWIN: Yes, including  
14 the placebo data because a lot of these changes will  
15 occur earlier than one year. So, it would make  
16 sense to me, you have placebo control trials this  
17 would be a critical element as well. So, we're  
18 interested in comparison with placebo and changes  
19 over time.

20 Maria?

21 DR. NEW: I just would like to address  
22 my question to Dr. Edwards. It must have been a  
23 shock to you to see no change in lipids in view of  
24 the rise in insulin?

25 DR. EDWARDS: May I suggest that we put

1 together two or three slides which summarize all of  
2 the data?

3 ACTING CHAIRMAN SHERWIN: Yes, I think  
4 we should give you a chance to respond. We'll take  
5 this up after lunch.

6 Bob?

7 DR. KREISBERG: I have several questions  
8 and then maybe we could cover some of them and let  
9 me come back to the others.

10 It seems to me that this issue of  
11 cardiovascular risk is important, even though the  
12 comparative data suggests that it is as good as  
13 other sulfonylureas. That doesn't necessarily mean  
14 that it is safe, just that it is as safe as other  
15 drugs that are currently approved. Because the drug  
16 involves the ATP sensitive potassium channel which  
17 influences a phenomenon called conditioning or pre-  
18 conditioning response to ischemia, the question is  
19 do you have any studies showing whether your drug  
20 influences the response to ischemia, either in  
21 experimental animals or in any other setting?

22 DR. FUHLENDORFF: We have not studied  
23 ischemia, but we have studied the affinity on the  
24 ATP sensitive potassium channel, both in heart and  
25 in beta cell. There was 100 to 400-fold potency

1 difference or affinity difference. So, the affinity  
2 was much higher to the beta cell than the heart.  
3 That's called tissue selectivity. We have no  
4 studies of ischemia.

5 ACTING CHAIRMAN SHERWIN: By the way,  
6 have you looked at brain as well?

7 DR. FUHLENDORFF: Yes, we have looked at  
8 brain as well. The affinity of repaglinide in brain  
9 is the same as it is in the beta cell.

10 DR. KREISBERG: The studies were not  
11 designed really to look at cardiovascular endpoints  
12 and I don't think that there are sufficient patients  
13 enrolled, considering what the projected frequency  
14 of a clinical endpoint would be to come to any  
15 meaningful conclusion about whether this drug does  
16 or does not predispose to cardiovascular endpoints.  
17 I think that this is an important issue to be  
18 addressed in ongoing studies by the firm should this  
19 drug receive approval and actually be used in  
20 patients because I don't think that's addressed  
21 here.

22 The other thing that I would like to  
23 talk to you about is actually getting back to this  
24 issue of the variability in the plasma levels of the  
25 drug, vis-a-vis the biologic response in the

1 patient. It suggests to me that while 99 percent of  
2 this drug is protein bound, that may be in the  
3 aggregate what it is. But have you ever looked in  
4 individual patients to see what the variability is  
5 in protein binding, to see whether some of the  
6 variation in the response has to do with a greater  
7 free fraction of the drug. I assume that free is  
8 what is biologically active in this drug. Whether  
9 there is a varying free fraction of the drug that  
10 accounts for a variation in biologic responsiveness.

11 A follow-up on that is simply to say  
12 that in your drug interaction studies, it looks to  
13 me like of four drugs that you evaluated, three of  
14 them were competing for a common hepatic pathway and  
15 only one, warfarin, might have been a drug in which  
16 you were looking at competition regard to binding on  
17 albumen. It seems to me that there must be other  
18 drugs that you could evaluate that would compete  
19 with repaglinide for binding sites on albumen.

20 DR. WHISNANT: I think we can only take  
21 those as good suggestions. We have not seen any  
22 evidence -- just to return to the question that Dr.  
23 Cara originated, we've not seen any evidence that  
24 the highly variable plasma levels of this drug,  
25 whether bound or -- well, total plasma levels

1 measured correlate with clinical toxicity events.  
2 In fact, we reanalyzed the information from the US  
3 long-term safety trial, study 49, looking for  
4 whether or not variability in steady state levels  
5 correlates with cardiovascular events. The fact is,  
6 it doesn't.

7           So, we are perfectly happy to pursue the  
8 suggestions that you're offering on a mechanistic  
9 basis in order, perhaps, you know in the future, to  
10 develop some more rational bases. But the clinical  
11 correlate, however, is going to be very difficult  
12 for us because therapeutic drug monitoring for  
13 hypoglycemic agents is certainly a new field, to say  
14 the least. It's not the norm and it has not been  
15 the way this drug or other drugs has been developed.  
16 So, we take your suggestions as a future  
17 development, but I'm not sure we have specific  
18 therapeutic drug monitoring or specific albumen  
19 binding fraction data to help with the dosing of the  
20 drug at the present time.

21           ACTING CHAIRMAN SHERWIN: In that  
22 regard, are you able to measure free drug?

23           DR. WHISNANT: What is the specificity  
24 of the new LCMS assay with regard to -- can we  
25 answer that question?

1 DR. HANSEN: Kristian Hansen, Novo  
2 Nordisk.

3 We are not able currently to measure the  
4 free fraction. What we measure is total drop in  
5 plasma, okay? Obviously, we have a bound fraction  
6 which is pretty high.

7 What I'd like to point out -- it's a  
8 very good point you make, but this drug is actually  
9 a highly clearance drug. Obviously, if there is  
10 variations in the free fraction, that will be  
11 rapidly clear for the bloodstream. So, that,  
12 perhaps, de-emphasizes a bit the protein  
13 interactions you're referring to.

14 ACTING CHAIRMAN SHERWIN: Roger?

15 DR. ILLINGWORTH: To extend the drug  
16 interaction question, since the drug is metabolized  
17 by a cytosol 3A4 system, have you looked at drug  
18 interactions with cyclosporin, erythromycin,  
19 ketaconazole -- drugs that metabolize by the same  
20 system?

21 DR. STRANGE: The short answer is that  
22 there has been no specific drug interaction trials  
23 performed. We have done a very detailed post hoc  
24 analysis with 3A4 inhibitors, ketaconazole, that  
25 patients in the long-term trial who happen to be on

1 those agents. We have seven treatment exposure  
2 years concomitantly with repaglinide in 18 patients.  
3 Only two of those patients had any events of  
4 hypoglycemia which is the only dose related event we  
5 have been able to find. Two out of 18 is actually  
6 less than our baseline rate in all patients.

7 So, it's not the specific interaction  
8 trial, but it is evidence that we don't have any  
9 clinically relevant interactions.

10 DR. MOLITCH: And conversely -- the  
11 effect of those drugs? How about the effects on  
12 those other drugs? The converse of that, not the  
13 effect on repaglinide but the effect on these other  
14 drugs, including estrogens?

15 DR. STRANGE: That hasn't been looked  
16 at. What we've looked at is adverse events in those  
17 patients and we haven't seen anything that's  
18 different from what we expect in all the treatment  
19 experience we have with repaglinide.

20 We have also in the 64 trial, which we  
21 mentioned before that we measured drug exposures in  
22 a reasonable number of patients, 120 patients, we  
23 found that the exposures attained concomitantly with  
24 3A4 substrates did not differ from the rest of the  
25 patients.

1                   ACTING CHAIRMAN SHERWIN:   Mark?

2                   DR. MOLITCH:   I guess coming back to  
3                   this issue of the free drug.  Although we realize  
4                   that this is a somewhat new experience for oral  
5                   hypoglycemic agents if, in fact, you did show a  
6                   correlation of free levels with the biological  
7                   activity, it might actually be not only interesting  
8                   but a therapeutically useful target just like we  
9                   measure other drug levels.  Given the wide dose  
10                  range that we're seeing here -- at least the wide  
11                  area under the curve and the wide dose range in  
12                  safety that you're providing for us, that in fact,  
13                  perhaps in some patients may need to go into higher  
14                  doses and so much lower doses depending on the free  
15                  drug level for that patient.  Maybe that's the way  
16                  it should be titrated rather than a fixed oral dose  
17                  for the patient.

18                  DR. WHISNANT:  Certainly, the fact is  
19                  that response to drugs like this are highly  
20                  variable.  In fact, response to insulin is highly  
21                  variable, as you all know.  So, any way in the  
22                  future that we can dissect the variability of that  
23                  response, we would certainly see as a future study  
24                  of the mechanistic aspects of this drug.

25                  Dr. Fossler has some help for us about

1 this?

2 DR. FOSSLER: I think you're forgetting  
3 your in vitro work, which I think is the most  
4 important aspect of your drug interaction studies.  
5 You know, they did some fairly good in vitro work  
6 which showed quite clearly, the interaction with 3A4  
7 substrates and that's in the labeling. So, you  
8 know, the current state-of-the-art right now and the  
9 Agency's opinion based on just recent guidances that  
10 have been issued is that if you show an interaction  
11 in vitro, we can use that in the labeling and that's  
12 fairly predictive.

13 DR. MOLITCH: Part of my concern also  
14 with the total drug levels that we're seeing and the  
15 great variability is in your statement that you  
16 think it's safe in patients with renal  
17 insufficiency. There clearly was a rising level at  
18 the lowest creatinine clearance levels on 20 or so  
19 moles per minute, or 7.3 meters squared. I think  
20 that given that you only had six subjects, given the  
21 degree of variability, that I would really -- I  
22 don't think that you can say this without a larger  
23 number of subjects being looked at to look at the  
24 cumulation of drug, a considerably larger number of  
25 subjects.

1 DR. KREISBERG: If I could make a  
2 suggestion that's sort of a corollary of what has  
3 been going on. One of the things I think the firm  
4 could do is actually look at indices of insulin  
5 sensitivity in these patients to see whether that  
6 determines what the response is to a particular dose  
7 of the drug. That would correlate what we know to  
8 exist in type 2 diabetic patients and that is a  
9 varying degree of insulin resistance.

10 DR. WHISNANT: The only piece of data  
11 that I can give you for sure is that C peptide  
12 levels, fasting C peptide levels at entry and during  
13 study do not correlate with hypoglycemia frequency  
14 in this trial and do not predict response, actually.

15 ACTING CHAIRMAN SHERWIN: Maria?

16 DR. NEW: I just would like to suggest  
17 that a possible explanation for variability is in a  
18 drug which is metabolized by a cytochrome p450  
19 system and which has a very large clearance. Since  
20 the cytochrome p450s are genetically programmed and  
21 very variable among individuals, that that's  
22 probably the explanation. You could test that,  
23 actually, by giving atypical cytochrome p450  
24 metabolized drug in individuals that are widely  
25 varied in their drug levels and see if that's the

1 difference.

2 DR. WHISNANT: Variability both in the  
3 liver and the gut and there's a well known system  
4 now. So, that's a future trial that perhaps would  
5 help us.

6 DR. NEW: Yes.

7 DR. CARA: But would that explain the  
8 individual variability?

9 DR. NEW: You know --

10 DR. CARA: I mean, the CV is over 60  
11 percent.

12 DR. NEW: Yes. José, the thing I'm most  
13 acquainted with is the difference in the cytochrome  
14 p450s that metabolize cortisol. They're extremely  
15 variable. We delude ourselves when we think that we  
16 give a program dose and pediatricians per kilo per  
17 meter square. You really have to measure the  
18 clearance and the degradation to know what dose to  
19 give.

20 DR. CARA: Sure.

21 DR. NEW: The point I keep making about  
22 children, you know, we keep saying that we have to  
23 scale down the dose in children because they're  
24 smaller. But in fact, they metabolize faster and  
25 they need a bigger dose.

1 DR. CARA: But these issues bring up  
2 important other questions which relate to -- you  
3 know, you talk about titration. What is your  
4 definition or your proposed definition as the  
5 endpoint of dose titration?

6 DR. WHISNANT: It was defined  
7 experimentally in the clinical trials. As  
8 designed, titration means begin at .5 milligram dose  
9 with each meal. Assess morning fasting plasma  
10 glucose response after 10 days to 14 days, and  
11 adjust upward by doubling if the patient has not  
12 achieved a target fasting plasma glucose of 160 or  
13 140. The target fasting plasma glucose was the same  
14 during the dose titrations for both repaglinide and  
15 for the comparator drug in those trials. So, it's  
16 an empiric definition within the context of the  
17 experimental design and the dose titration steps  
18 were .5, one, two, and four.

19 DR. CARA: I guess my concern is that  
20 there's no stopping the titration point. Because if  
21 you say, "gee, you know, I got down to a fasting  
22 blood sugar of 150", what's to say that doubling the  
23 dose is not going to decrease it to 120? And that  
24 quadrupling it will lead to a further fasting blood  
25 sugar level? I mean, everybody is going to end up

1 on the maximum dose in view of the fact that in  
2 diabetes, we typically try to get the blood sugar  
3 down to as normal a level as possible.

4 We admit that one of the weaknesses in  
5 the comparator trial design as carried out was that  
6 there was, if you will, a stopping rule in those  
7 trials that said "titrate to this level and stop,  
8 and do not change the dose during the maintenance  
9 phase of the trial." We admit that the trial design  
10 was carried out that way primarily for regulatory  
11 purposes in order to show that we are not  
12 statistically worse than the comparator drug.

13 ACTING CHAIRMAN SHERWIN: Now, what did  
14 you use as your basis for that comparator? I'm just  
15 curious about that. In other words, was it fasting  
16 glucose or --

17 DR. WHISNANT: Morning fasting plasma  
18 glucose. That's correct.

19 ACTING CHAIRMAN SHERWIN: Yes, because  
20 that would trouble me a little bit because you're  
21 comparing now drugs that have a longer duration of  
22 action which will affect the fasting. Whereas, you  
23 might be giving more drug here to reduce the fasting  
24 since it doesn't theoretically last quite as long.  
25 So, in other words, you would think that this drug

1 would work more in the interim during the day and a  
2 little less during fasting, and using your fasting  
3 as your comparator. I think that's a little bit of  
4 a problem.

5 DR. WHISNANT: Dr. Sherwin, we admit  
6 that the data are what they are. The study showed  
7 that we were equivalent within the definition of not  
8 being worse than .6 grams percent of HbA<sub>1c</sub> at 12  
9 months. That's the reason the trials were carried  
10 out and therefore, the data have to speak to only  
11 that conclusion.

12 A variety of other things could be done  
13 now that we understand a lot more about this new  
14 dosing paradigm which really is a part of the  
15 discussion that Dr. Fleming is going to lead us to.

16 ACTING CHAIRMAN SHERWIN: Sure.

17 DR. FLEMING: I do think it would be  
18 helpful to show the outcome of dose adjustments that  
19 occurred in the comparative studies. If you could  
20 pull those slides up showing what happened with  
21 repaglinide and with the comparator drugs?

22 ACTING CHAIRMAN SHERWIN: Do we really  
23 know -- I'm just curious how long this drug actually  
24 works?

25 DR. WHISNANT: It works for over a year.

1                   ACTING CHAIRMAN SHERWIN:  No, no, no,  
2                   no.  I didn't mean it that way.  I'm sorry.  I'm  
3                   sorry.

4                   What I meant was in terms of giving a  
5                   dose and then seeing how long the effect lasts.  I'm  
6                   confused.  Is this a drug that's over at 10:00 at  
7                   night and doesn't work anymore?  You know, what's  
8                   the duration of action of the drug?  Because I  
9                   didn't see any data that really told me that.

10                  DR. WHISNANT:  Well, that is also built  
11                  into the points for discussion that Dr. Fleming has  
12                  designed.  Let me just refer you back to the three  
13                  paneled slide that Dr. Strange showed in the  
14                  clinical pharmacology studies.

15                  If you accept plasma insulin as the  
16                  kinetic endpoint, if you will, for this drug then  
17                  plasma insulin curves follow the same as the meal  
18                  related physiologic, if you will, plasma insulin  
19                  curves that are normally seen without drug.  
20                  Therefore, that establishes a kinetic for the drug.  
21                  If you ask for the kinetic of the blood glucose  
22                  response, remember that was also shown on the three  
23                  paneled slide that Dr. Strange showed you.  In fact,  
24                  the plasma glucose response also follows the, if you  
25                  will, meal related, normal physiologic pattern.

1                   ACTING CHAIRMAN SHERWIN: Well, I'm not  
2     sure.

3                   DR. WHISNANT: Okay.

4                   ACTING CHAIRMAN SHERWIN: In other  
5     words, because the glucose levels are different in  
6     the two -- you know, they're not the same, I'm not  
7     exactly sure that that proves that duration is short  
8     or long or whatever. I'm not sure that you wouldn't  
9     see where I would -- you know, if you could show me  
10    the same pattern with a comparator with lower  
11    glucoses after the comparator and then show me the  
12    profiles and show me differences between the drugs,  
13    maybe then I could accept that. But I'm not sure  
14    that I can accept that under the -- I saw no data  
15    personally that really totally convinced me what the  
16    duration of action of the drug was.

17                  DR. WHISNANT: Maybe we should go to the  
18    issues discussion that's been --

19                  ACTING CHAIRMAN SHERWIN: Well, I can  
20    stop here and we can go back to that issue later on.  
21    That's my impression when I looked at the data that  
22    I've seen so far.

23                  DR. FLEMING: Well, I do think it's very  
24    important to understand how these comparative  
25    studies were conducted. It's important in

1 understanding the comparability of dosing that  
2 occurred between the two groups in each trial. Now  
3 I received from the company some data which showed  
4 at what doses patients ended up in the comparative  
5 studies and that allows us to look at both the  
6 comparator and repaglinide itself in each study.

7 I don't know if you've been able to put  
8 your hands on that particular transparency, but it  
9 is very interesting that apparently, there is almost  
10 a superimposability of the distribution of doses  
11 used during the observation period with respect to  
12 both repaglinide and the comparator. In other  
13 words, approximately half the patients ended up at  
14 the high dose of repaglinide and the comparator and  
15 it went down the line. About 25 percent ended up at  
16 the -- it would be the two milligram repaglinide  
17 dose or the second highest comparator group. Each  
18 group seemed to correspond very closely.

19 Now, I think it would be worth  
20 explaining what the dosage rules were in the  
21 comparative studies. This will, I think, reflect  
22 some approximation of clinical practice going to Dr.  
23 Cara's excellent question about whether one could  
24 perhaps go overboard and drive patients into the  
25 ground by over-prescribing. I don't think there is

1 an indication that that happened in these  
2 comparative studies.

3 DR. WHISNANT: Certainly, to the  
4 contrary actually, Dr. Fleming. Thanks very much.  
5 The dose titration paradigm, let me repeat  
6 carefully. Patients were started on .5 milligrams  
7 after a basal evaluation period, either a run-in  
8 drug free period or a crossover -- patients were  
9 started on .5 milligrams. After an average of ten  
10 days, patients had a fasting plasma glucose  
11 assessment. If their target had not been achieved  
12 -- that is, 160 or 140 -- then they were dose  
13 escalated. After another week to 10 days, they were  
14 reassessed and they were dose escalated again. So,  
15 those patients who achieved the target in either  
16 drug stopped at the dose where they achieved that  
17 target and that was their, if you will, "maintenance  
18 dose" from then to the end of the trial without  
19 changing dosing.

20 So, in effect, for both treatments, we  
21 got what we set out to get. We titrated to  
22 equivalent endpoints and proved equivalence for  
23 these kinds of patients. Which patients ended up  
24 out of the randomized, double-blind design -- which  
25 patients ended up at the lowest dose level were

1 those that were obviously more responsive to the  
2 lowest dose.

3 Yes?

4 DR. MARCUS: How many fasting plasma  
5 glucose determinations went in after the ten days,  
6 just one? Or did you get daily for a few days?

7 DR. WHISNANT: A single one.

8 DR. MARCUS: One fasting glucose made --  
9 okay.

10 DR. WHISNANT: It's the normal dosing  
11 paradigm, titration paradigm of diabetics.

12 DR. MARCUS: No, it's not. I mean, when  
13 we see patients in clinic, we ask him to bring in a  
14 book documenting the last several weeks of home  
15 glucose monitoring. And we can see that, you know,  
16 on one day, they may have been 90 and on other days  
17 they may have been 340. So, I mean, that's --

18 DR. WHISNANT: And we would have done  
19 the trial that way if the Agency would accept BGMS  
20 as endpoints.

21 DR. CARA: But you're not really  
22 describing a dose response study then.

23 DR. WHISNANT: This is not a dose  
24 response, sir. This is a dose titration study to  
25 equivalence.

1 ACTING CHAIRMAN SHERWIN: Correct.

2 That's right.

3 DR. CARA: Well, do you have any dose  
4 response studies?

5 DR. WHISNANT: Yes, we do. We showed  
6 you two dose response studies.

7 DR. CARA: The non-comparator studies?

8 DR. WHISNANT: One was a placebo  
9 controlled phase II dose comparison over .25  
10 milligrams to four milligrams --

11 DR. CARA: Right.

12 DR. WHISNANT: -- fixed dose for  
13 patients who were randomized to fixed dose for four  
14 weeks --

15 DR. CARA: Right.

16 DR. WHISNANT: -- with primarily a blood  
17 glucose endpoint. Then we showed you a six month  
18 trial randomizing patients to placebo, one milligram  
19 and four milligrams, where patients were evaluated  
20 with glycemic control, HbA<sub>1c</sub>. In those studies, we  
21 believe we've showed you an adequate response over  
22 that dose range.

23 DR. KREISBERG: I don't think so. If  
24 you would look on your page 22 and your figure 5.6,  
25 and on page 36 your figure of 6.3 -- which actually

1 is the same study just displayed a little bit  
2 differently -- it seems to me that the response kind  
3 of plateaus as you go from .5 to two, you do have  
4 the sense and maybe you get a little bit better  
5 response when you're up at four milligram dosing but  
6 the numbers of patients in these studies are  
7 relatively small. I really wonder if you're not on  
8 a plateau somewhere between 0.5 and two. If you  
9 look at your figure 6.3, the mean glucose change for  
10 the half, one and two milligram doses are the same.

11 DR. WHISNANT: If you turn this figure  
12 upside down and subject it to an Emax modeling  
13 exercise, I believe the statisticians, clinical  
14 pharmacologists in the room will agree that this  
15 more-or-less fits an Emax model dose relationship  
16 for this drug. We do admit that you've got a lot of  
17 response out of the lower doses. You might ask  
18 what's the rationale for having chosen .5 milligrams  
19 as the lowest marketed dose of the drug, if you  
20 will. That is because a substantial portion of  
21 patients, actually 25 percent of patients in the  
22 titration trials at first step, achieved response.  
23 But in this trial and others, the .25 milligram dose  
24 was not nearly as effective in terms of a responder  
25 analysis.

1                   You might also conclude that two  
2 milligrams might be enough for a very large  
3 percentage of patients. We would not disagree with  
4 that. In fact, we've identified a subset of  
5 patients in which two milligrams seems to be an  
6 ideal starting dose.

7                   DR. KREISBERG: Well, do you think that  
8 the mean reduction in glucose for the four milligram  
9 dose, taking into consideration the number of  
10 patients that have been studied, is significantly --  
11 and I mean statistically significantly different  
12 than the values attained with .5 to 2.0?

13                  DR. WHISNANT: Actually, the study was  
14 not designed to test statistically the difference  
15 between two milligrams and four milligrams. It was  
16 designed to test statistically the dose response  
17 over the dose range. Those statistics are clear and  
18 included in the report.

19                  DR. MOLITCH: I'd like to come back to  
20 this fasting glucose business and also your mean  
21 blood glucose levels. Figure 5.4 looks at the  
22 average blood glucose profiles. Are these the blood  
23 glucose samplings that made up the mean glucose  
24 profiles that we're talking about? Because the  
25 sampling -- then dividing by 24 or whatever?

1                   ACTING CHAIRMAN SHERWIN:  Where is this?

2                   DR. MOLITCH:  Figure 54 on page 19.  Are

3                   those the sampling times for that glucose profile?

4                   DR. WHISNANT:  Sir, that's a different

5                   trial.

6                   DR. MOLITCH:  But is that the nature of

7                   the sampling profile?

8                   DR. WHISNANT:  What you would do --

9                   DR. MOLITCH:  What made up the mean

10                  glucose levels?  What sampling times?

11                  DR. WHISNANT:  You would do a 20-point

12                  profile on each patient.

13                  DR. MOLITCH:  And when were they done?

14                  DR. WHISNANT:  The time intervals for

15                  the 20-point profiles?

16                  DR. MOLITCH:  Yes, exactly.

17                  DR. WHISNANT:  What are the time

18                  intervals?

19                  DR. STRANGE:  It's most easily

20                  demonstrated on the curves.

21                  DR. MOLITCH:  Which curve?

22                  DR. STRANGE:  Well, I demonstrated them.

23                  It's at 8:00, 8:30, 9:00, 9:30, 10:00, and then

24                  11:00, 12:00, 1:00, 1:30 --

25                  ACTING CHAIRMAN SHERWIN:  Maybe you

1       could put that slide up?

2                   DR. STRANGE:  -- around the meals.

3                   DR. MOLITCH:  Yes, but see, that's my  
4       point that your mean blood glucose of the level is  
5       essentially around the time of the meals when we're  
6       seeing the action of this drug.  We're then ignoring  
7       about ten hours during the night when this drug is  
8       probably not having very much activity when blood  
9       glucose levels could be considerably higher.

10                  DR. STRANGE:  Was a value determined at  
11       12:00 in the evening?

12                  DR. MOLITCH:  Yes, a single value.  But  
13       we're talking about taking all of these values and  
14       then dividing by 24 or whatever the number is.  So  
15       that, it's not a true 24-hour day curve.

16                  DR. STRANGE:  It's not this curve.  It's  
17       the 64 trial.

18                  Forward, forward, there.  Oh, you can  
19       actually not see the dots.  But you can see the  
20       indentations in the curve exactly where the sampling  
21       times are.

22                  DR. MOLITCH:  So that, it's very much a  
23       weighted curve towards the daytime rather than the  
24       nighttime where you probably are having much less  
25       drug action?

1 DR. STRANGE: It is. It is a weighted  
2 curve centered around the meal peaks, but there are  
3 values one hour before the beginning of a meal. If  
4 you note the very far left peak of them, you'll see  
5 -- if you follow the -- you have a 30 minute value,  
6 a one hour value, a one-and-a-half hour value, two  
7 hour value, and a four hour value. I think there's  
8 also a three hour value actually, but a four hour  
9 value which is one hour before the next dose at five  
10 hours following the first dose. So, you have a  
11 fairly good representation of the whole profile.

12 I agree with you that you don't have a  
13 good representation of the profile from 12:00 in the  
14 night until 8:00 in the morning. But if you look at  
15 the curve, the numbers are so low on the repaglinide  
16 profiles that, you know, it doesn't really matter.

17 DR. CARA: But what if you look at the  
18 glucose profiles?

19 DR. STRANGE: Could you go forward one  
20 slide? Next one.

21 There are the glucoses in the night.  
22 The change if you follow the green line -- the area  
23 we're now arguing about is this area from this data  
24 point to this data point which is only a data point  
25 there and a data point there. If you look at the

1 difference between that value and that value, either  
2 this way or that way is not going to influence the  
3 average of that curve over 24 hours to any big  
4 degree.

5 DR. MOLITCH: Well, if you had the same  
6 sampling interval over the course of that time that  
7 you did in the morning, sure it will. Then divide  
8 by the total number of points, of course it will.  
9 So, it greatly influences --

10 DR. STRANGE: Just let me understand  
11 what you're saying. You say that these eight hours  
12 of the curve where we see a decrease of 20  
13 milligrams per deciliter or something -- you say  
14 that because we don't have many values in there  
15 where people did not take meals but slept in their  
16 bed, so that's going to influence the average over  
17 24 hours --

18 DR. MOLITCH: Certainly.

19 DR. STRANGE: -- to a great degree?

20 DR. MOLITCH: Absolutely.

21 DR. STRANGE: Okay.

22 ACTING CHAIRMAN SHERWIN: It would give  
23 us the mean of all numbers, yes.

24 DR. MOLITCH: Part of the problem is  
25 that, we're getting back at this fasting glucose as

1 using it as a measure of efficacy of this drug,  
2 since the drug doesn't last overnight, presumably.  
3 There was a suggestion in one of these slides  
4 earlier that maybe, in fact, with the four milligram  
5 dose that there may still be some drug levels out by  
6 the time of that fasting -- in the morning.

7 How do you think that this drug is  
8 working to lower the fasting glucose levels? What  
9 mechanism?

10 DR. WHISNANT: Well, by the same  
11 mechanism that for many, many years, people whose  
12 glycemic control was provided by a single dose of  
13 insulin a day. When patients get better glycemic  
14 control, their fasting plasma glucoses in the  
15 morning are decreased. We're not, you know, trying  
16 to say that we understand the natural history of  
17 islet cell function enough to know why that occurs.  
18 That's an issue for a very sophisticated analysis of  
19 diabetes biology.

20 The fact is that when you dose this  
21 agent with a very small dose, the .5 milligram dose,  
22 where within a few hours the drug is completely gone  
23 and the insulin profile is back to meal related  
24 insulin profile, that over four weeks you do get  
25 better glycemic control of those patients as

1 reflected in the fasting plasma glucose.

2 ACTING CHAIRMAN SHERWIN: Yes, I mean, I  
3 agree with you. Clearly, the glucose levels are  
4 better. The question was just to get a better  
5 understanding of how. Because if you look at the  
6 fluctuations during the meal, depending on the  
7 graph, almost in each case the fasting glucose is  
8 substantially lower. Then if you look at the  
9 fluctuations with the mean, the fluctuations are not  
10 grossly different as compared to placebo.

11 So, it looks as if -- I mean, almost  
12 that the drug is not -- it's supposed to be working  
13 during the day to diminish meal induced fluctuations  
14 and yet, the changes are not that dramatic during  
15 that period when the drug is supposedly doing its  
16 major work. So, the question was sort of whether  
17 this drug might have other effects that we don't  
18 totally appreciate? Or that its effects over time  
19 diminish with respect to meal induced changes.

20 DR. WHISNANT: We certainly hope that  
21 the drug has other effects besides enhancing the  
22 physiologic profile of insulin and therefore, has  
23 other potential for, you know, long-term  
24 modifications of the natural history of diabetes.  
25 Obviously, the obvious answer to the question of

1 does this drug provide glycemic control is that it  
2 does provide glycemic control over a year. Unless  
3 we were doing something as a consequence of this  
4 enhancing physiologic insulin profile -- that is  
5 reflected in morning fasting plasma glucose -- we  
6 wouldn't get glycemic control over --

7 ACTING CHAIRMAN SHERWIN: No. I guess  
8 the point is the uniqueness of the medication. You  
9 know, it's not that it doesn't work. You've  
10 demonstrated a change. It's just is this different  
11 than any other drug, or does all these drugs improve  
12 glucose control a little bit? Fasting glucose  
13 diminishes because glucose production has changed,  
14 and then everything else we see is much the same.  
15 No matter how you get to that point, ultimately, the  
16 drug is working like every other drug, or is there  
17 something unique about this drug? That's what I  
18 would -- that's the point.

19 DR. WHISNANT: We appreciate your  
20 offering us futuristic advice about that. If we  
21 weren't here on an accelerated approval basis, maybe  
22 we might have some more patients to show you.

23 ACTING CHAIRMAN SHERWIN: Sure. No, I  
24 understand that. No, I understand that point too.

25 Have you looked at, let's say, two days,

1 or one or two days when things are starting out much  
2 the same way? You know, if you don't look at, you  
3 know, long-term effects, short-term effects in  
4 people with diabetes, are there differences then  
5 that are much more obvious?

6 DR. WHISNANT: Differences compared to  
7 other drugs, you mean?

8 ACTING CHAIRMAN SHERWIN: To placebo.

9 DR. WHISNANT: In short-term studies,  
10 the enhancement of the physiologic insulin profile  
11 is very clear over placebo, including an alteration  
12 of the morning fasting plasma glucose a day or even  
13 two days after the drug has already been  
14 discontinued. So, there is effect on the biology of  
15 the pathology, if you will, of diabetes but those  
16 kinds of studies have not been included in this  
17 submission.

18 ACTING CHAIRMAN SHERWIN: Okay.

19 DR. MOLITCH: It seems that if part of  
20 the unique action of the drug is its short activity,  
21 then it clearly would lend itself to some sort of  
22 combination with other agents that would have a  
23 longer action overnight, such as a long acting  
24 sulfonylurea at night with this drug during the day  
25 or long acting insulin at that time with this drug

1 in the morning. Those might be future studies that  
2 could be done unless you have anything like that  
3 ongoing.

4 DR. WHISNANT: I thank you very much.  
5 If you're available as a consultant, we'd be happy  
6 to include you in the design of those studies. I  
7 actually have with me, a variety of plans for future  
8 questions of this type, you know. Because of the  
9 differential binding and because of the potency of  
10 this drug, does it actually rescue patients who are  
11 inadequately treated with sulfonylureas, for  
12 instance? Does it rescue patients like the  
13 metformin patients? I mean, that's one case that  
14 we've demonstrated already. Will it rescue  
15 trivitisone failure patients?

16 Those studies are in our designs, you  
17 know, and at some point during this discussion we  
18 can talk specifically about what suggestions you  
19 have for our future with this drug. We are also  
20 planning to present here this morning, a three to  
21 four year study primarily at least targeted toward  
22 providing additional safety information regarding  
23 cardiovascular events, but during which we will  
24 collect long-term natural history data about this  
25 drug. So, I mean, there are a number of these kinds

1 of questions that will be very helpful to us.

2 ACTING CHAIRMAN SHERWIN: With regard to  
3 the issue you just spread out, you showed us data of  
4 the total group and you showed us data, I think, of  
5 naive patients which showed perhaps -- it looked to  
6 me like a greater response relative to placebo.

7 DR. WHISNANT: Yes?

8 ACTING CHAIRMAN SHERWIN: I don't  
9 remember seeing sulfonylurea failure patients as a  
10 subgroup. The question is, in people that fail in  
11 sulfonylureas, how do they respond to this drug?

12 DR. WHISNANT: Actually, the trial  
13 database includes a lot of those patients that you,  
14 as clinicians, might say are sulfonylurea failure  
15 patients. I mean, we haven't used that word in our  
16 entry criteria for the trials. But in the entry  
17 criteria particularly for the comparator trials, we  
18 have said patients who are inadequately treated on  
19 other therapies, including sulfonylureas, many, many  
20 of those patients, Dr. Sherwin, come in with HbA<sub>1c</sub>'s  
21 of nine or 10, or 11, or 12. If you remember Dr.  
22 Strange's distribution plot of the endpoints --

23 ACTING CHAIRMAN SHERWIN: Right.

24 DR. WHISNANT: -- of those HbA<sub>1c</sub>'s,  
25 we're talking about, in effect, failure patients.

1 In that population of patients, we get a 1.6 to 2.9  
2 delta HbA<sub>1c</sub>. Admittedly, depending on the inherent  
3 responsivity of the patient or where that patient is  
4 in the natural history of the disease, we can show  
5 you very clearly, data that say that not only did  
6 not do the naive -- that is, not previously treated  
7 patients -- respond better, but the patients who  
8 were previously treated still respond although the  
9 mean response is not as great.

10 ACTING CHAIRMAN SHERWIN: Do you think  
11 you could, at some point, just show us the actual  
12 data in terms of the failure patients? I mean, the  
13 problem I guess is, a failure patient is not quite a  
14 failure patient. Once you take the patient off the  
15 drug --

16 DR. WHISNANT: Right.

17 ACTING CHAIRMAN SHERWIN: -- usually  
18 they get a little worse. So, if you're comparing  
19 that to a placebo, you'll see a difference.

20 The question, I guess, is in patients  
21 who are inadequately controlled who you then just  
22 compare that to continuing on the sulfonylurea  
23 versus using this drug instead, which is what you  
24 would do clinically, do you have any data with  
25 regard to that?

1 DR. WHISNANT: Well, actually, that's  
2 inherent in the design --

3 ACTING CHAIRMAN SHERWIN: In the  
4 comparator study, right?

5 DR. WHISNANT: It's inherent in the  
6 design of the comparator trials. Remember that the  
7 patient population was recruited. That over 80  
8 percent of them in those trials were previously  
9 treated patients. Then they were randomized to  
10 either continuation of, in many cases, a  
11 sulfonylurea or glyburide in a random double-blind  
12 fashion. So, we have data to show that transferring  
13 patients to repaglinide who are those kinds of  
14 previously treated, high HbA<sub>1c</sub>, long history  
15 patients were actually completely satisfactorily  
16 maintained on this drug for over a year.

17 ACTING CHAIRMAN SHERWIN: Right. But  
18 there's not a difference between them and the  
19 sulfonylurea group, right? So, it's hard to tell  
20 from the data. That's why I'm trying to say  
21 clinically, if you have a patient who is not  
22 responding to a drug, often what you'll do is switch  
23 them to another drug and see if they do better. I  
24 can't eke out from the data thus far, you know, how  
25 that would sort out.

1 DR. HIRSCH: That's really another  
2 question. I mean, if you're saying -- well, let me  
3 go back a minute.

4 I assume that what we're talking about  
5 here is a short acting oral agent, and that's a very  
6 desirable thing to have presumably for the treatment  
7 of, or prevention of hypoglycemia. That's one set  
8 of analyses which has --

9 DR. WHISNANT: Yes, sir.

10 DR. HIRSCH: -- been the brunt of what  
11 you've presented --

12 DR. WHISNANT: We'll show you some more  
13 of that.

14 DR. HIRSCH: -- and the major thrust of  
15 that. But the issue of whether this is now a kind  
16 of rescue drug for those who have failed from other  
17 treatments, that would have to be presented  
18 differently so that we could analyze that specific  
19 issue and see how often that's the case and how  
20 useful that is.

21 Now, I'm assuming the thing works  
22 because A<sub>1c</sub> hemoglobins go down the same with this  
23 drug, unless this is a protein bound drug. Unless  
24 it's some really weird thing that this affects the  
25 glycosylation of hemoglobin and I'm sure you've

1 thought about that --

2 DR. WHISNANT: Yes.

3 DR. HIRSCH: -- and ruled it out so that  
4 the drug doesn't do anything of that sort. But what  
5 I'm most interested in now is the spontaneous  
6 hypoglycemia kind of people, or the induced  
7 hypoglycemia. In their nature, do they have lower  
8 A<sub>1c</sub> hemoglobins than the others? Are these the  
9 group who are trying very hard to manage themselves?  
10 What is the cost psychologically and in terms of  
11 compliance of taking a drug three times a day rather  
12 than once a day?

13 DR. WHISNANT: Excellent questions. Let  
14 me try to address very briefly the first part of  
15 your question. Thank you for your support.

16 The fact is, the comparator trials were  
17 not designed or carried out in such a way to show  
18 superiority. They were titrated to equivalence.  
19 Therefore, the chance of showing that this  
20 physiologic insulin dosing profile compared to a  
21 sustained long acting insulin secretagogue is  
22 different. They weren't designed to show that.

23 We didn't do comparator trials  
24 randomized to a low dose versus a high dose of our  
25 drug, and a low dose versus a high dose of a

1       comparator drug, say, glucatrol XL. We also didn't  
2       yet do trials to say if you take patients who are  
3       titrated to some submaximal dose of another  
4       secretagogue. Say in that profile shown up there  
5       on that slide, two-thirds sulfonylurea maximum dose  
6       and then you titrate in repaglinide as an addition,  
7       what additional response will you get by this  
8       different binding site, more potent if you will,  
9       secretagogue? And then as a final phase, to further  
10      titrate those patients to maximum dose to see what  
11      maximum effect we can really get. That hasn't been  
12      done. We admit that. So, we're happy to pursue  
13      those kinds of second line, third line product  
14      expansion kinds of questions based on what we've  
15      learned about the drug.

16                    With regard to the subpopulation that  
17      might be sensitive to hypoglycemia, we actually have  
18      some slides for the next session here.

19                    Do you want me to go to those at the  
20      present time?

21                    Can I go to hypoglycemia section of the  
22      presentation, toward the end? My staff is doing a  
23      better job of finding slides than I am of explaining  
24      them, I think.

25                    To answer your question specifically,

1 Dr. Hirsch, in the 065 trial where we compared  
2 placebo one milligram and four milligrams, we  
3 actually looked at the frequency of hypoglycemia,  
4 percent of patients having hypoglycemia based upon  
5 their baseline HbA<sub>1c</sub>. Most diabetologists have seen  
6 this information and say "what's new? We knew that  
7 all along." Because the way it turns out is that  
8 previously treated patients who have a low HbA<sub>1c</sub>,  
9 say below seven or below eight, have a pretty low  
10 frequency of hypoglycemia naturally and not much of  
11 a hypoglycemia problem. You know, we're talking  
12 about 10 maybe 20 percent, one out of five patients  
13 on the average of those patients would have  
14 hypoglycemia. A little bit of dose response in this  
15 low HbA<sub>1c</sub> subset, but essentially no response in the  
16 high HbA<sub>1c</sub> subset.

17 On the next slide, I'll show you the  
18 same information for naive patients where the  
19 percentage of patients developing hypoglycemia is  
20 not only dose related, but occurs much more in the  
21 low HbA<sub>1c</sub> patients than in the high baseline HbA<sub>1c</sub>'s.  
22 So, one could rationally design therapy, customize  
23 therapy, if you will, for patients based upon their  
24 risk of developing hypoglycemia which, by the way,  
25 is probably the same set of variables that predicts

1 response.

2 DR. MOLITCH: Show me that -- slide,  
3 please?

4 DR. WHISNANT: Go back.

5 DR. MOLITCH: Why is there a 15 percent  
6 risk of hypoglycemia in those with baseline  
7 hemoglobin A<sub>1c</sub> over ten with placebo therapy? I'm  
8 not sure I understand that.

9 DR. WHISNANT: That's a very strong  
10 effort.

11 DR. MOLITCH: Why should it be any?  
12 Even in the nine to 10 group, you've got  
13 substantial --

14 DR. WHISNANT: Because if you follow  
15 patients with diabetes on placebo, they report  
16 hypoglycemia.

17 DR. MOLITCH: Which makes me wonder  
18 about your criteria for hypoglycemia.

19 ACTING CHAIRMAN SHERWIN: Excuse me.  
20 Would you be able to talk in the microphone?

21 DR. WHISNANT: I mean, I don't mean to  
22 be simplistic but that's the only answer I know.  
23 That if you follow patients on placebo, they report  
24 hypoglycemia.

25 ACTING CHAIRMAN SHERWIN: Let's get back

1 to the --

2 DR. MOLITCH: That's getting to be  
3 worrisome.

4 ACTING CHAIRMAN SHERWIN: -- definition.

5 DR. WHISNANT: Right. What's your  
6 definition.

7 ACTING CHAIRMAN SHERWIN: That's one of  
8 the questions I wanted to get to is how do you  
9 define hypoglycemia?

10 DR. WHISNANT: Hypoglycemia is reported  
11 as any symptom where the patient interprets the  
12 symptom as hypoglycemia or where the doctor  
13 synthesizes what the patient has reported and checks  
14 hypoglycemia on an adverse reaction form. All  
15 hypoglycemias are reported as mild to moderate  
16 unless the patient required assistance for managing  
17 that event, in which case it's reported as severe.

18 ACTING CHAIRMAN SHERWIN: Yes. So, the  
19 key to the question -- because obviously, the mild  
20 and moderate hypoglycemia is extremely difficult to  
21 quantify. Consequently, in fact, the DCCT try to  
22 avoid looking at those issues because of the  
23 difficulties in quantifying. What about the  
24 instance of severe hypoglycemia requiring help? Do  
25 you have data to look at that specific issue?

1 DR. WHISNANT: Severe and --

2 ACTING CHAIRMAN SHERWIN: Severe  
3 hypoglycemia as defined by the DCCT was a patient  
4 requiring help by another person, glucagon, or a  
5 hospital admission.

6 DR. WHISNANT: Right. Assistance  
7 required hypoglycemia did not occur with repaglinide  
8 in these trials.

9 ACTING CHAIRMAN SHERWIN: And how about  
10 the comparitors?

11 DR. WHISNANT: It occurred a number of  
12 times that you can count on one or two hands, but it  
13 was not a frequent event. I think it was not a  
14 frequent event in part because these were not  
15 intensification kinds of trials. They were trials  
16 where patients' drugs were not pushed.

17 ACTING CHAIRMAN SHERWIN: Now, the next  
18 issue somewhat related to that is the data that we  
19 saw, my impression was that most of the patients we  
20 saw had fasting glucoses that were quite high and  
21 generally in a range, in fact, where beta cell  
22 responses are not that good.

23 So, were there differences in response  
24 to drug depending on the level of fasting glucose or  
25 glycohemoglobin -- we're looking at percentages

1 here, but not absolute numbers. So, were the  
2 majority of patients here, do they have fasting  
3 glucoses over 150? You know, I'm trying to get a  
4 sense of whether there's a difference in response  
5 depending on the level of glucose, or we're dealing  
6 with a homogeneous group with most of their fasting  
7 glucoses above 180, for example, to start out.

8 DR. WHISNANT: You're dealing, first of  
9 all, with a heterogenous group of patients who had  
10 relatively high blood glucoses based upon the  
11 inclusion criteria for the trials. The patients  
12 were picked greater than 160 --

13 DR. STRANGE: For an HbA<sub>1c</sub> less than 12.  
14 For sulfonylurea treated patients HbA<sub>1c</sub> less than  
15 12.

16 DR. WHISNANT: We're talking about the  
17 minimum fasting plasma glucose was 160, right?

18 DR. STRANGE: What trial are we talking  
19 about?

20 ACTING CHAIRMAN SHERWIN: Well, I'm just  
21 trying to get a sense because most of the data I saw  
22 had mean fasting glucoses over 200. So, it looked  
23 like the majority of patients that were treated had  
24 very poorly controlled diabetes. We know that from  
25 other drugs that that's the group that seems to have

1 the best responses for some ungodly reason, perhaps  
2 because there's more play in the system. I just  
3 wondered whether people that were a little better  
4 controlled, whether their response was somewhat  
5 different?

6 DR. WHISNANT: So, you'd like to see a  
7 delta FPG versus baseline FPG in order to look at  
8 the correlation --

9 ACTING CHAIRMAN SHERWIN: I'm just  
10 curious. Yes. In other words, I just don't have a  
11 good feel for, you know, the group. My sense is  
12 that we're dealing with people that are very poorly  
13 controlled and we're seeing an improvement.

14 DR. WHISNANT: Well, actually, the range  
15 of HbA<sub>1c</sub>'s for the trial population, for instance in  
16 the 65 trial which is the trial we've already showed  
17 you the distribution -- the range of HbA<sub>1c</sub>'s was all  
18 the way from seven, which is the lower limit allowed  
19 in the trial, up to 12 which was the upper limit  
20 allowed in the trial.

21 ACTING CHAIRMAN SHERWIN: Right.

22 DR. WHISNANT: The mean in most of the  
23 trials turned out to be above nine. So, we're  
24 dealing with a relatively poorly controlled  
25 population of diabetics.

1                   ACTING CHAIRMAN SHERWIN: Right. Now,  
2           those patients have much poorer beta cell function  
3           in general. So, my question is, does the drug have  
4           different effects when your beta cells are working  
5           better? You know, it could go either way. I mean,  
6           I just don't have a good sense of -- you know, I  
7           looked at curves before with glucose levels  
8           extremely high and I saw some insulin responses to  
9           mixed meals. But it may be that the responses are  
10          much greater and therefore -- I mean, then the  
11          question of hypoglycemic risk, you know, may be  
12          different depending on the status of disease you're  
13          dealing with and the starting out levels of glucose.  
14          You know, in other words, in patients who are naive  
15          --

16                   Now the diagnosis of diabetes has gone  
17          down so that now we're talking about a fasting  
18          glucose of 126. Now, if you use this drug in a  
19          population with a fasting glucose of 130 that has  
20          retained beta cell function, is the response of the  
21          beta cells going to be different to this  
22          secretagogue. I mean, those are the issues --

23                   DR. WHISNANT: I'll help you out as much  
24          as I can, Dr. Sherwin. The facts that we know are -  
25          -

1                   ACTING CHAIRMAN SHERWIN: And I realize  
2 that you have moved ahead quickly and I --

3                   DR. WHISNANT: That's okay.

4                   ACTING CHAIRMAN SHERWIN: -- realize,  
5 you know, that -- it's not a criticism. It's just  
6 that I'm raising questions.

7                   DR. FLEMING: Well, I think there are  
8 some data to answer that question.

9                   DR. WHISNANT: Yes, there are.

10                  DR. FLEMING: In terms of the hemoglobin  
11  $A_{1c}$ , they have formally looked at an interaction  
12 with baseline  $A_{1c}$ . Now, can you pull this figure  
13 up? I'm not sure how to tell you which one it is.

14                  ACTING CHAIRMAN SHERWIN: What page is  
15 it?

16                  DR. FLEMING: Oh, this is in part of  
17 their NDA submission. I don't know whether you have  
18 it. It's figure 7.2 in your --

19                  DR. WHISNANT: Well, actually, I can  
20 tell you -- I don't have the figure even in the back  
21 of slides. But I can tell you that the correlation  
22 between  $HbA_{1c}$  at baseline and  $HbA_{1c}$  at conclusion of  
23 the trial is almost one because really bad patients  
24 who have very high  $HbA_{1c}$ 's get about a one to one-  
25 and-a-half delta improvement with this drug. Low

1 HbA<sub>1c</sub> patients get proportionately a little more  
2 than that but the correlation coefficient is still  
3 very high. And as you would suspect. I mean,  
4 that's why you're asking the question.

5 That is, in part, reflected in the  
6 baseline HbA<sub>1c</sub> data that I showed you for  
7 hypoglycemia. It's the naive patients with low  
8 HbA<sub>1c</sub>'s who tend to be the most responsive and  
9 therefore, have either relatively low blood glucoses  
10 measured by meter readings, or who have relatively  
11 rapid decrement in blood glucose, either of which  
12 gives you symptomatology.

13 ACTING CHAIRMAN SHERWIN: Yes, that  
14 would have been my guess. So, the one thing that,  
15 you know -- if this drug is more potent in terms of  
16 the beta cell, in terms of that, I mean one of the  
17 issues will be to look carefully at the hypoglycemic  
18 risk in that subpopulation of patients. Compared to  
19 some other drugs, you know, in terms of what the  
20 relative risks might be because it looked fairly  
21 high for the patients that were well controlled to  
22 start with.

23 So, whether there should be a warning  
24 for people with regard to type who are well  
25 controlled already in terms of hypoglycemic risk. I

1 mean, I guess that's sort of where I'm heading.

2 DR. CARA: As a follow-up to that  
3 question, you took patients that were in suboptimal  
4 control, put them on therapy, and the goals of  
5 therapy were still suboptimal. No, really, okay?

6 DR. WHISNANT: Okay.

7 DR. CARA: I mean, do you have any  
8 evidence to show what happens when you push those  
9 patients further in terms of trying to get  
10 reasonable control, i.e., fasting blood sugars in  
11 the 80 to 150 range in terms of the incidence of  
12 hypoglycemia?

13 DR. WHISNANT: What we do have is  
14 indirect evidence to answer that question because we  
15 did randomize placebo control blinded trial of a  
16 lower dose versus a full dose. So, for that  
17 heterogeneous patient population that includes some  
18 of those naive, low HbA<sub>1c</sub> patients, we know what the  
19 relative risk of hypoglycemia is relative to HbA<sub>1c</sub>  
20 and to dose. You're absolutely correct that we've  
21 identified a subset of patients for relatively more  
22 responsive and have relatively more hypoglycemia.  
23 It is those patients that we would suggest should be  
24 titrated starting at .5 milligrams.

25 Frankly, the rest of the patients who

1 have higher HbA<sub>1c</sub>'s and who previously treated  
2 whether controlled or not, have perfectly  
3 acceptable, normal, almost placebo controlled levels  
4 of hypoglycemia. That was on the two stack bar  
5 charts that I showed you. So, we're dealing with a  
6 subset of patients who have relatively high  
7 response, are sensitive to the drug, have low  
8 HbA<sub>1c</sub>'s at baseline and therefore should be titrated  
9 carefully. That's in the labeling.

10 DR. CARA: Another question related to  
11 just the opposite phenomena maybe. That is, have  
12 you looked at the percent of patients that are not  
13 responders?

14 DR. WHISNANT: Have we looked for --

15 DR. CARA: I mean, what percent of  
16 patients do not respond to therapy?

17 DR. WHISNANT: We know -- yes, the shift  
18 curve that we showed you for 65 actually shows you  
19 that. It shows you the distribution of final  
20 HbA<sub>1c</sub>'s around 50 percent of the patients. It shows  
21 you what percentage of patients achieve seven or  
22 eight or nine at the end of a six month trial.

23 Can we go back to that?

24 DR. CARA: But that's not really my  
25 question because you started out with patients with

1 high glycohemoglobins to begin with. It's hard to  
2 tell from that whether they ended up better or  
3 worse.

4 DR. WHISNANT: Well, it's obviously hard  
5 to take a patient with a 10 and make them a seven.  
6 Most drugs don't do that.

7 DR. CARA: But if you take a patient  
8 with a 14 and make them an 11, that's still a fairly  
9 good response. Whereas, if you look at it in the  
10 absolute value, it's still high.

11 DR. WHISNANT: Oh, we understand that.  
12 The mean change in that study is about 1.6 to 1.8,  
13 and actually goes up to 2.9 for the naive, highly  
14 responsive patients, right?

15 DR. CARA: Okay.

16 DR. WHISNANT: So, on that shift curve  
17 we showed you, if we can find that --

18 DR. CARA: I just want a clear answer.

19 DR. WHISNANT: Well, the answer is that  
20 the decrement in people's glycemic control -- the  
21 endpoint in people's glycemic control does depend on  
22 where they start. That's for sure.

23 DR. MOLITCH: What percentage of people  
24 are non-responders stratified by baseline hemoglobin  
25 A<sub>1c</sub>? At each hemoglobin A<sub>1c</sub> level, what percentage

1 of people are non-responders?

2 DR. WHISNANT: Non-responders as  
3 measured by --

4 DR. MOLITCH: A change in hemoglobin A<sub>1c</sub>  
5 of greater than a half percent, or less than half  
6 percent.

7 DR. WHISNANT: Oh, virtually everybody  
8 changes by that much.

9 DR. MOLITCH: What's the number?

10 DR. WHISNANT: We'll get you the  
11 distribution of numbers over lunch but --

12 DR. MOLITCH: Thank you.

13 DR. WHISNANT: -- that's an achievable  
14 target.

15 DR. MOLITCH: Well, I'd like to see  
16 that.

17 DR. WHISNANT: Thank you. That's an  
18 easy one.

19 ACTING CHAIRMAN SHERWIN: Yes. What  
20 percentage of patients overall -- I mean, I know  
21 that most of them start out high and therefore,  
22 didn't reach that point -- reach the point of less  
23 than seven percent hemoglobin A<sub>1c</sub>?

24 DR. WHISNANT: We showed you that on the  
25 shift curve.

1                   ACTING CHAIRMAN SHERWIN: Percentage of  
2 the overall group?

3                   DR. WHISNANT: I can only show you by  
4 study. I don't know for everybody. But here's the  
5 50 percent -- this is cumulative frequency of  
6 patients. Fifty percent of the patients at the end  
7 of the study in the high dose were below eight --  
8 below 7.9 actually -- and for the lower dose group,  
9 it was a slightly larger endpoint for 50 percent of  
10 the patients. If you want to know what fraction of  
11 patients achieved seven, it's small.

12                  ACTING CHAIRMAN SHERWIN: It looks about  
13 20, 25 percent though.

14                  DR. WHISNANT: I mean, it's a number but  
15 remember that this is the distribution of patients -  
16 - this is the end distribution for the placebo  
17 patients, but it really represents the distribution  
18 of all patients at the beginning of the study  
19 because the placebo patients didn't change. Right?  
20 A little bit, but I mean, this is approximately the  
21 distribution of the HbA<sub>1c</sub>'s at the beginning.

22                  We can actually plot it that way if you  
23 want to see that so that you can see, not on an  
24 individual patient basis, but statistically as a  
25 group, that's the kind of magnitude that occurs at

1 various levels of baseline HbA<sub>1c</sub>.

2 ACTING CHAIRMAN SHERWIN: From what you  
3 said before, if 20, 25 percent reach a level less  
4 than seven percent, my impression was that the  
5 percent of people that had hypoglycemia was about 50  
6 percent or something like that from the bars that  
7 you showed?

8 DR. WHISNANT: No, it depends on the  
9 subset of patients that you're looking at.  
10 Actually, for naive patients who are sensitive to  
11 the drug and have low baseline HbA<sub>1c</sub>'s, patients who  
12 would start down there somewhere below eight, those  
13 are responsive patients and over half of them would  
14 develop hypoglycemia to any drug. So, you have to  
15 be careful of those patients. But for patients  
16 above an HbA<sub>1c</sub> of eight and who were previously  
17 treated, probably later in the stage of their  
18 disease, then the frequency of hypoglycemia in that  
19 group is down on the order of one out of four, one  
20 out of five.

21 ACTING CHAIRMAN SHERWIN: Bob?

22 DR. KREISBERG: This gets back to a  
23 point that I was trying to make previously about the  
24 differences in doses. If you look at the cumulative  
25 distribution in response to the one milligram and

1 the four milligram dose, I'm not impressed that  
2 there is a substantial difference in the response,  
3 which gets into the issue of what particular dose  
4 the firm is going to recommend for the treatment of  
5 patients with type 2 diabetes.

6 I believe that in your material, that  
7 the maximum dose is going to be four milligrams,  
8 four times per day. But it looks to me like that  
9 you get most of what you're going to need without  
10 going to four milligrams four times a day. Do you  
11 want to continue to recommend the four milligram  
12 dose?

13 DR. WHISNANT: The four milligram dose  
14 has been shown, first of all, to be a safe dose  
15 given four times a day. In fact, one-fifth of the  
16 maximum dose that we've studied in a group of  
17 patients, the four milligram dose does give you an  
18 increment of responsivity both for an individual  
19 patient and for groups of patients. I mean, you're  
20 already probably up at ED80, ED90 or something like  
21 that when you pass two.

22 As a matter of fact, some of the dosing  
23 discussions that we've been involved in would  
24 indicate that for previously treated patients,  
25 particularly those that are relatively lower risk of

1 hypoglycemia, that we probably should recommend  
2 those patients just start on two milligrams and  
3 that's their dose. Because as you say, we're  
4 probably up somewhere on the dose response curve.  
5 It is true that the difference between one milligram  
6 and four milligrams is bigger for the naive  
7 patients, the more responsive patients. But for  
8 previously treated patients, it could be that four  
9 milligrams is just an increment of both efficacy in  
10 terms of percent of responder patients as well as an  
11 increment for an individual patient. We agree with  
12 that.

13 DR. EDWARDS: And the F90s are shown  
14 here --

15 DR. WHISNANT: That's the difference in  
16 dose for HbA<sub>1c</sub> over six months for the 65 trial.  
17 So, there's a difference. But when you look at all  
18 treated patients or when you take out this subset  
19 and look at the previously treated patients, then  
20 you know, once you pass one milligram, you've got a  
21 lot of the effect. It's a very potent drug.

22 DR. HIRSCH: I just think we shouldn't  
23 factor out of the equation, the compliance issue and  
24 assume automatically that if the A<sub>1c</sub> hemoglobin is  
25 low that means that they're in earlier stage of the

1 illness or more sensitive or whatever. There may  
2 also be the issue of how compliant people are which  
3 hits to the central issue of whether you want to try  
4 to solve the problem by making a greater puzzle.  
5 They have to take something four times a day instead  
6 of once or twice a day.

7                   So, you have no way, I suppose, of  
8 monitoring compliance or couldn't during these  
9 studies?

10                   DR. WHISNANT: Well, we certainly agree  
11 -- I mean, we do have a compliance number and we'd  
12 be happy to share that with you as we have with the  
13 Agency. These studies were based on a more than 80  
14 percent compliance of doses based on pill counts,  
15 based on histories. So, we know that probably if  
16 you don't take the drug, it probably won't work as  
17 well and we give you that.

18                   We also give you the fact that in this  
19 country, the standard care still reflects that most  
20 patients have an HbA<sub>1c</sub> above nine -- most patients  
21 of diabetes -- and that most patients don't have  
22 screening eye exams and yearly HbA<sub>1c</sub>'s and so forth.  
23 So, I mean, we actually understand that part of the  
24 reason patients go into our trials with poor control  
25 is because of poor care. You know, we're not up to

1 standard yet. Our company would hope that if we can  
2 -- 90 percent of patients to more than 80 percent of  
3 the doses in the 65 trial.

4 We hope that we can actually turn around  
5 this business of, you know, compliance being worse  
6 with multiple doses of drug per day because if we  
7 tie a dose of a diabetic drug to a glucose load at a  
8 meal, maybe the doctors will use that to teach  
9 patients about their disease and teach patients to  
10 do something about that peak of glucose with each  
11 meal. That would be sort of our hope that we would  
12 actually contribute something to the natural history  
13 and care of patients with this disease. It's not an  
14 approvability issue.

15 DR. MARCUS: Well, I think it is. I  
16 wish, actually, there would be a little more  
17 emphasis on this issue because we actually approved  
18 -- or we recommended approval of an altered insulin  
19 about a year ago, specifically for the reason -- in  
20 large part for the reason that it offered a degree  
21 of flexibility to patients in terms of their timing  
22 of meals. That is a feature, I think a cardinal  
23 feature, of this agent that has not even been  
24 mentioned today. So, I think it is worth a mention.  
25 I think if a person is going to skip lunch, or if a

1 person is going to have an additional meal, it does  
2 give you an opportunity to interact with the effects  
3 of that meal, or lack of that meal more efficiently  
4 than you could --

5 DR. HIRSCH: But there's no data on that  
6 at all.

7 DR. CARA: But you haven't actually  
8 determined whether you can actually do that with  
9 this drug.

10 DR. HIRSCH: That's correct. We have  
11 data on normals, but no data on diabetics skipping  
12 meals.

13 DR. WHISNANT: Actually, we are going to  
14 show you some data.

15 DR. HIRSCH: Okay.

16 DR. WHISNANT: We have a short session  
17 designed on, if you will, the dosing paradigm and  
18 the implications of dosing paradigm for skip a meal,  
19 different flexibility, and what the implications of  
20 that are. I will respond and say thank you very  
21 much. We've actually been accused of being  
22 something called the "oral humalogue". You know, if  
23 that paradigm makes sense to people who try to take  
24 care of patients with diabetes, then we're happy to,  
25 you know, help with that.

1 DR. NEW: Actually, that was going to be  
2 my question. In the use of the rapid acting  
3 insulin, in children at any rate, there's been a  
4 great satisfaction reported by parents and children.  
5 I'm wondering whether your patients in the clinical  
6 trials have reported a satisfaction of knowing that,  
7 you know, if they're going to go out to dinner, they  
8 take the Prandin 15 minutes before they're going to  
9 eat. What kind of a response do you get  
10 psychologically and satisfaction-wise from that?

11 DR. WHISNANT: I can only give you  
12 indirect evidence and a promise. The indirect  
13 evidence is that the dropout rates in our trials,  
14 certainly versus placebo, were very satisfactory.  
15 The promise is that we're building in quality of  
16 life assessments into the phase III BM4 trials that  
17 are being done.

18 I'm sorry I can't answer anymore detail  
19 than that, but it's obviously a very important  
20 question in terms of the impact of a new therapy  
21 like this on care.

22 ACTING CHAIRMAN SHERWIN: José?

23 DR. CARA: You recommend giving the  
24 Prandin 15 minutes before the meal. What's that  
25 based on?

1 DR. WHISNANT: It's based on a study  
2 that was done showing that there's no difference in  
3 the plasma profiles if you dose 30 minutes before,  
4 15 minutes before, or at the time of the beginning  
5 of the meal. I mean, obviously, we realize that a  
6 meal event is not a one minute event --

7 DR. CARA: Right.

8 DR. WHISNANT: -- but you can mark in a  
9 trial, the initiation of the meal. Then you can do  
10 the dose then, or 15 minutes before, or 15 minutes  
11 before that. So, we suggest that there's a 30  
12 minute window based on PK, not based on a  
13 therapeutic endpoint.

14 DR. CARA: So, I mean, there's no basis  
15 to say that the patient can't take the medication  
16 immediately before eating?

17 DR. DAMSBO: It can be taken at the same  
18 time --

19 DR. WHISNANT: Yes, it can. I said  
20 that.

21 DR. DAMSBO: -- show that taking it at  
22 time zero and time minus 15 and --

23 DR. WHISNANT: Is the same thing.

24 DR. DAMSBO: -- gave the same profile.  
25 It can be taken within 15 --

1 DR. CARA: Same profile, okay. I mean,  
2 just in terms of compliance issues, I think that you  
3 will get a lot more compliance if you say you can  
4 take this immediately before eating versus taking it  
5 15 minutes before and then having to wait 15  
6 minutes.

7 DR. WHISNANT: Oh, we understand that,  
8 Dr. Cara, but you also very well -- I know you  
9 understand that when you're carrying out clinical  
10 trials, you have to specify how you want things done  
11 in order to get consistency of data.

12 DR. CARA: Sure.

13 DR. WHISNANT: So, our answer to the  
14 question is the vast bulk of the data were generated  
15 on a minus 15 schedule for purposes of consistency  
16 and clinical trials, but there is a PK trial that  
17 Dr. Damsbo might be able to find the data on to show  
18 you that minus 30, minus 15, and zero are the same.

19 DR. CARA: If you could find that, that  
20 would be nice.

21 DR. WHISNANT: We'll show you that.

22 ACTING CHAIRMAN SHERWIN: Mark, I'm  
23 sorry.

24 DR. MOLITCH: I have a question that's  
25 not really been addressed previously. Viewing from

1 a relatively simple clinician's point of view, one  
2 of the concerns about using sulfonylureas in the  
3 past, over the years, that's never been proven or  
4 disproven that maybe their use helps to further  
5 exhaust the islet cell. I don't know if that's true  
6 or not true.

7                   You've made a lot about this lack of  
8 insulin exocytosis. What does this mean clinically  
9 to us if we're going to be giving this to patients  
10 from a mechanistic point of view? Does this have  
11 any effect on that controversy? I mean, so what?  
12 Why do I need to know about that?

13                   DR. WHISNANT: Well, what we hope it  
14 means is that a drug whose mechanism is as described  
15 would not -- the correlation in pharmacology is  
16 dump. We all know about drug dumping. You take a  
17 dose of drug. You know, because of a lipid meal or  
18 whatever, you know, sometime later you get this big  
19 surge of drug and you get a problem.

20                   What we hope is, because this drug is  
21 carefully modulated and as it approaches very low  
22 levels of glucose, we actually don't get any further  
23 release and you don't get any release that's  
24 independent of the channel mechanism. Whereas, with  
25 the other drugs if, for instance, you keep pushing

1 and pushing and pushing the glyburide dose, then at  
2 some concentration that Dr. Fuhlendorff actually  
3 showed you, the insulin will just release without  
4 regard to the channel modulating the thing at all.

5 So, the goal for us is to have a drug  
6 that's carefully modulated and to some extent, is  
7 modulated based on the glucose profile itself. So,  
8 what we hope we can show you is a safer profile  
9 relative to hypoglycemia frequencies, both in the  
10 elderly at night and for the population as a whole.  
11 We can also show you in that analysis that there is  
12 substantially fewer patients who have very low blood  
13 glucoses. If you count the number with BGMs below  
14 45, the number is very low compared to the  
15 comparator population.

16 Have we proven that this lack of  
17 exocytosis is directly related to a lower frequency  
18 or a lesser severity of hypoglycemia? No, we  
19 haven't proven that, but it's consistent with what  
20 we know about the mechanism of the drug.

21 ACTING CHAIRMAN SHERWIN: Could you  
22 speak into the microphone please? I'm sorry. I  
23 apologize for the setup. It's not ideal. I realize  
24 that.

25 DR. DAMSBO: This is a study performed

1 in type 2 diabetic patients given one milligram of  
2 repaglinide at the time zero, minus 15 or minus 30  
3 before a standardized meal. As you can see, the  
4 area under the curves is equivalent, as well as the  
5 Cmax.

6 DR. CARA: But what happens with the  
7 blood sugar?

8 DR. DAMSBO: The blood sugar is equally  
9 reduced. It's the same as the --

10 DR. CARA: Do you have that data? Do  
11 you have the blood sugar profiles?

12 DR. WHISNANT: Not here.

13 DR. DAMSBO: Not right here, no.

14 DR. WHISNANT: I mean, the curves in  
15 this, minus 30, minus 15, and zero study of drug and  
16 of insulin response, in response to that  
17 variability.

18 DR. CARA: Right. I mean, it makes  
19 sense that the degree of insulin response is going  
20 to be the same.

21 DR. WHISNANT: Right.

22 DR. CARA: The issue is whether the  
23 timing of the insulin response is such that you need  
24 to take the medication 15 minutes before the meal  
25 versus, you know, zero minutes before the meal.

1 DR. WHISNANT: I understand.

2 DR. CARA: That's the issue.

3 DR. WHISNANT: Because of the meal  
4 related effect on insulin --

5 DR. CARA: Right.

6 DR. WHISNANT: -- added to our drug  
7 related effect on insulin, do the two added up  
8 change the overall therapeutic effect in those  
9 patients?

10 DR. CARA: Right. And is there a  
11 greater incidence of hypoglycemia if you take it  
12 just before the meal versus 15 minutes? I mean,  
13 those are the sorts of issues that --

14 DR. WHISNANT: We understand that, Dr.  
15 Cara. Unfortunately, this is not a therapeutic  
16 trial, but we do, somewhere, have the BG response in  
17 those patients. Not for this trial.

18 For this trial?

19 DR. DAMSBO: Not for this trial.

20 DR. WHISNANT: Not for this trial.

21 ACTING CHAIRMAN SHERWIN: Okay.

22 Hopefully, we've grilled you enough right now, I  
23 think. Maybe you could take a break.

24 DR. WHISNANT: We thank you very much  
25 for your help, for your ideas. We're prepared to

1 move on with the rest of the presentation, depending  
2 on what Dr. Fleming would like to do.

3 ACTING CHAIRMAN SHERWIN: Dr. Fleming,  
4 would you like to address the first question and  
5 then we'll take a break for lunch?

6 DR. FLEMING: All right, very good.

7 ACTING CHAIRMAN SHERWIN: Or do you  
8 think that it's going to be --

9 DR. FLEMING: Yes, I think we might as  
10 well use the 15 minutes that we had counted on.

11 DR. WHISNANT: Unfortunately, our  
12 response to the first question is more than a 15  
13 minute response.

14 DR. FLEMING: Okay.

15 ACTING CHAIRMAN SHERWIN: Okay, that's  
16 important. What would you estimate your response to  
17 the first question?

18 DR. WHISNANT: I don't know. Probably  
19 2:30, 3:00.

20 ACTING CHAIRMAN SHERWIN: You made me  
21 nervous.

22 DR. WHISNANT: Actually, a good bit of  
23 your -- I started to say questions, but maybe  
24 interrogation is the right word.

25 ACTING CHAIRMAN SHERWIN: Right, right.

1 DR. WHISNANT: A good bit of this  
2 discussion relates to this question and maybe we  
3 could go faster based on that.

4 ACTING CHAIRMAN SHERWIN: Well, let's  
5 try to get it done in a half-hour.

6 DR. WHISNANT: Okay.

7 DR. FLEMING: Yes, I believe we have  
8 substantially dealt with many of the issues that  
9 could be covered under this point. We're starting  
10 with this as the first discussion point because,  
11 after all, this was the probably most attractive  
12 feature of the drug. That is, the potential for  
13 reducing hypoglycemia while achieving equivalent  
14 glycemic control.

15 Now, as you know, the studies were not  
16 specifically designed to demonstrate a difference in  
17 hypoglycemic potential or outcome, but we do have  
18 some data that are encouraging. It's clear that we  
19 do not have definitive proof that in clinical  
20 practice, particularly as patients are being more  
21 aggressively managed, that they will also experience  
22 a reduction in significant hypoglycemic episodes.  
23 So, we would propose that we look particularly at  
24 this question. The company obviously has some data,  
25 some they've already shown. Perhaps we could deal

1 with it fairly expeditiously.

2 DR. WHISNANT: Would you like us to move  
3 on?

4 ACTING CHAIRMAN SHERWIN: Yes, sure.

5 Would you prefer to come up here? Maybe  
6 it would be better. It's up to you.

7 DR. WHISNANT: Actually, I'm going to  
8 ask two of our staff to give a couple of prepared --  
9 an introductory perspective about this question and  
10 then to provide some specific information with  
11 regard to the kinetic profile, as well as to the  
12 further data on the hypoglycemia consequences of  
13 that kinetic profile. So, I'll just introduce and  
14 let them go to the podium. Then it will be easier  
15 for them to see their slides and so forth.

16 Dr. Wendell Cheatham is the medical  
17 director for Novo Nordisk in Princeton in the  
18 American affiliate office. Dr. Cheatham is at home  
19 in Washington where he was an endocrinologist for  
20 many years until we stole him away. He's going to  
21 provide the introductory perspective on this  
22 question relative to diabetes care.

23 Then Dr. Peter Damsbo who is the  
24 director of clinical research in our Copenhagen  
25 office will provide some data to help answer the

1 question.

2 Dr. Cheatham?

3 DR. CHEATHAM: Thank you, Dr. Whisnant.

4 Dr. Sobel, Dr. Fleming, Dr. Sherwin and  
5 distinguished members of the Advisory Board, what  
6 I'd like to do at this point is to set the stage for  
7 a discussion of the clinical relevance of  
8 repaglinide to the questions that are being asked at  
9 this point.

10 I don't need to belabor the point that  
11 we've recently added two million additional  
12 individuals to the roles of people who have diabetes  
13 in this country. Eighteen million individuals now  
14 and virtually all of those individuals who have been  
15 added have type 2 diabetes. That gives us  
16 approximately 16 million individuals with type 2  
17 diabetes, but the most important point that we need  
18 to pay attention to, as most of you who are  
19 educators and also have patients with diabetes, is  
20 that less than half of these individuals with  
21 diabetes are under any form of therapy. Beyond  
22 that, of the half that are under therapy, less than  
23 half of those are under appropriate therapy. So,  
24 less than one-quarter of the patients in this  
25 country with diabetes are being appropriately

1 treated for their diabetes.

2 Another important point to keep in mind  
3 is that more than half of the individuals with  
4 diabetes in this country are over the age of 60, 58  
5 percent, in fact, or some 10 million individuals.  
6 In another 12 years, for those of us who are part of  
7 the baby boom population that will swell the ranks  
8 of those who are in that age group, we're going to  
9 have some 24 million individuals with diabetes  
10 particularly because of the first point. Some 64  
11 percent of individuals by that time because of the  
12 growth in that segment of the population will be  
13 over the age of 60, some 15 million individuals in  
14 this country with diabetes.

15 We know about the several year history  
16 of a goal for control of diabetes being at a  
17 hemoglobin A<sub>1c</sub> of seven percent or below. The  
18 recommendation that intervention is definitely  
19 indicated when the hemoglobin A<sub>1c</sub> is at eight  
20 percent or above. Unfortunately, as our studies  
21 have indicated, just based on our recruitment of  
22 individuals for trials and also on population  
23 surveys and studies that have been published, the  
24 best results that we can get for hemoglobin A<sub>1c</sub> in  
25 this country, in a broad ranging population of

1 individuals with diabetes, is no less than 9.1  
2 percent which translates into an average blood sugar  
3 of at least 200 milligrams per cent or above. So,  
4 although we talk about individuals in our trials  
5 being poorly controlled, unfortunately, that's a  
6 profile of diabetes in the United States.

7 Possible reasons for inadequate therapy?

8 Well, delayed diagnoses. We know that that takes  
9 place. We know, in fact, that the average person  
10 with type 2 diabetes is diagnosed some five to eight  
11 years after they truly have developed the  
12 biochemical markers of the disorder. There's a low  
13 sensitivity to the seriousness of the disorder not  
14 only in the patient population, but also in the  
15 practitioners to a large extent. There's a fear of  
16 hypoglycemia with effective therapy and perhaps to  
17 some extent, we shouldn't necessarily stigmatize the  
18 practitioners for having a low sensitivity.

19 But after all, if you can raise the  
20 level of blood sugar by 100 percent to 200  
21 milligrams per deciliter and not impact  
22 symptomatology very much, but lower it by 20 percent  
23 below the given norm and individuals have  
24 significant problems with the symptomatology, then  
25 you would understand why individuals perhaps aren't

1 willing to necessarily jump off and start treatment  
2 right away, especially with the treatment  
3 armamentarium that we have available to us at this  
4 point in time for individuals who are just crossing  
5 the threshold into diabetes.

6           Fear of hypoglycemia is real because  
7 those of us who are clinicians recognize that you  
8 always enter a period of limbo between the time  
9 point when you've diagnosed a person with diabetes,  
10 you've attempted diet and exercise therapy and those  
11 have failed. Their target hemoglobin A<sub>1c</sub> is not  
12 being met but you know through experience that if  
13 you start oral agents, and in the case of our  
14 traditional oral agents, the sulfonylureas, you're  
15 bound to have a high frequency of hypoglycemia and  
16 severe hypoglycemia at that.

17           We have non-compliance which, of course,  
18 is a problem that we are attempting to impact. I'll  
19 say something more about that a little later. We  
20 have primary failure of medications. Often,  
21 individuals have started on medications and there's  
22 a psychological comfort in putting a person on a  
23 medication and perhaps even lowering the hemoglobin  
24 A<sub>1c</sub> by a half or one percentage point, but still not  
25 achieving true control. Whether you want to call

1 that primary failure, or partial primary failure of  
2 course is a discussion of verbiage. We have  
3 secondary failure with individuals who go on oral  
4 hypoglycemic agents, the sulfonylureas  
5 traditionally, but we recognize that those drugs  
6 have a duration of activity, or at least usefulness,  
7 if you look at them critically for no more than  
8 approximately eight years.

9           The clinical dilemma then is one where  
10 we know that we are to achieve near normalization of  
11 blood glucoses. That is the clinical aim to prevent  
12 the late diabetic complications. Indeed, the goal  
13 of seven percent or below is a translation from the  
14 diabetes control and complications trial, which  
15 although it dealt with type 1 diabetes, we know at  
16 least that the microvascular complications of that  
17 trial, we believe -- scientific observation  
18 translates itself into hemoglobin A<sub>1c</sub>. In fact,  
19 population studies again relate retinopathy,  
20 neuropathy, nephropathy, and limb amputation  
21 directly to surveys of hemoglobin A<sub>1c</sub>.

22           We've experienced an inability to reach  
23 these near normal blood glucoses with oral  
24 hypoglycemic agents, not necessarily due only to  
25 primary or secondary failure. Often, it's a chosen

1 under-dosing to avoid hypoglycemia because as was  
2 previously stated. Thus, we actually may be  
3 trading, in some cases, long-term complications  
4 because we want to avoid hypoglycemia or we're  
5 dealing as well with a psychological resistance to  
6 moving forward to the next stage of therapy which  
7 would be insulin therapy.

8 At this point, I'm gong to turn the  
9 discussion over to my colleague, Dr. Peter Damsbo,  
10 who will discuss for you the clinical dilemma and  
11 the application of our studies in practical terms to  
12 a potential answer to the clinical dilemma at least  
13 at one particular level.

14 DR. DAMSBO: Thank you, Dr. Cheatham.

15 Ladies and gentlemen, I would like to  
16 start out with the slide that Dr. Reit started out  
17 with this morning which is an ADA statement saying  
18 "severe hypoglycemia is the major complication of  
19 sulfonylurea therapy. Elderly patients are more  
20 susceptible to hypoglycemia particularly when they  
21 have tendency to skip meals or when renal function  
22 is impaired."

23 Let me just after this, shortly  
24 summarize some of the pharmacology and  
25 pharmacokinetic resource we have as of now. Dr.

1 Fuhlendorff told us this morning about the reduced  
2 effect on insulin release at low blood glucose  
3 levels and at the same time, there was no direct  
4 exocytosis contrary to existing sulfonylureas. From  
5 the pharmacokinetic beta percented by Dr. Strange,  
6 we had a short action of drug and an incident that  
7 reverts to the control levels. Meal related dosing  
8 is the concept that came out of it. This with a  
9 tablet-a-meal; no meal, no tablet.

10 I'll try to dig a little further into  
11 this to illustrate the short action here on the next  
12 slide. As you can see here, we have on the left  
13 lower panel repaglinide profile. This is the four  
14 milligram dose given as a single dose. You have the  
15 rapid absorption and you have the rapid elimination  
16 of the drug. So, after two or three hours, there's  
17 hardly any drug left. When it comes out to the  
18 lunchtime here -- these columns here shows the  
19 breakfast and lunchtime -- there's very little drug  
20 left.

21 This gives together with a meal rise to  
22 insulin profiles like this. The red one is the  
23 insulin profile. The green one is the placebo  
24 control. It's across all studies in the same  
25 patients. As you can see, there is a rise in the

1 insulin and the insulin comes all the way back to  
2 the control level before the next meal. That's a  
3 very good indication of a similar insulin profile at  
4 the time where you enter to the next meal. That is  
5 that you have a short action on the beta cell.

6 This is translated into a glucose  
7 profile that you see on the lower panel here at the  
8 right. This is the placebo control. When you have  
9 given four milligrams of repaglinide, you have a  
10 dose profile like this. As you can see, the  
11 following meal has this same profile, so to speak.  
12 It's just shifted downwards. Actually, as you might  
13 also be able to see from this, the increment in  
14 glucose is higher after the treatment, indicating  
15 that the drug has stopped its action on insulin.

16 The idea here is that you need insulin  
17 when you eat. To dip further into that one on the  
18 next slide, we conducted a study where we looked at  
19 the fixed and the mixed meal concept. Could you  
20 give the drug in a fixed way three times a day with  
21 three meals and compared it to the group that has  
22 shifting meals, going from two, to three, to four?  
23 Will they be able to obtain the same glycemic  
24 control over time? It was a three-week study in-  
25 house. At the end of the study, the patients were

1 followed in a tight -- blood glucose profile. As  
2 you see here, the red line is the two meals and two  
3 tablets. The green line, three meals, three  
4 tablets, and four meals and four tablets. As you  
5 can see, the profiles follow, so to speak, the  
6 dosing and the meals nicely. The green one with the  
7 three here and the four meals was an extra snack  
8 given out here in the evening.

9 DR. CARA: What's the dose?

10 DR. DAMSBO: The dose here was -- the  
11 same dose for all patients was one milligram.

12 DR. KREISBERG: Are these normal people?

13 DR. DAMSBO: Those are diabetic  
14 patients.

15 ACTING CHAIRMAN SHERWIN: Was the  
16 earlier data diabetes also?

17 DR. DAMSBO: These have a combination of  
18 naive and sulfonylurea. But it's a fairly mild  
19 type --

20 ACTING CHAIRMAN SHERWIN: No, I meant  
21 the previous slide.

22 DR. DAMSBO: Yes. That was in type 2  
23 diabetic --

24 ACTING CHAIRMAN SHERWIN: Also?

25 DR. DAMSBO: Yes.

1                   ACTING CHAIRMAN SHERWIN:   Okay.

2                   DR. DAMSBO:   So, when looking at this,  
3                   it's quite obvious that you can give the same.  You  
4                   can dose the drug either two, three, or four times  
5                   with the meals and obtain the same glycemic control.

6                   To then go a little further into the  
7                   possibilities of using this drug in the setting when  
8                   you omit a meal, we conducted a study in comparison  
9                   to glyburide.  These were patients who were taken  
10                  in.  They were treated, titrated to the maximum  
11                  effective dose.  After three weeks, they entered a  
12                  stabilization period.  Those patients who had a  
13                  blood glucose below 145 or 140 entered the last  
14                  phase.  Then the day that this profile was made,  
15                  lunch was omitted.  In the repaglinide group, only  
16                  two doses were given with the two meals, and in the  
17                  glyburide group two doses were given as well before  
18                  breakfast and before dinner.

19                  But now the patients omitted lunch and  
20                  the impact, as you can see here, is that the  
21                  glyburide group, which is the red one here, comes  
22                  down.  Just before lunchtime, the blood glucose  
23                  keeps on going down actually.  It goes further down  
24                  here and it stays down until the next meal comes and  
25                  increase the blood glucose.  In comparison to

1 repaglinide, you have the blood glucose that comes  
2 up, goes down, and stays at the level of normal,  
3 around 90 milligrams per deciliter, and remains down  
4 there. The effect of this on the safety side was  
5 that there was in the glyburide group, six patients  
6 who experienced hypoglycemic events during that  
7 afternoon, and no patients in the repaglinide group.

8           One other little detail I would like to  
9 draw your attention to is that as was mentioned  
10 earlier, I think by Dr. Molitch, was that what  
11 happens during night? As you can see here, we have  
12 an increase during the night in the blood glucose of  
13 both the glyburide, but also even more pronounced by  
14 the repaglinide group. So, during the night, the  
15 blood glucose levels are higher with the repaglinide  
16 group than it was with glybenlimide, although the  
17 glycemic control -- the area under the curve,  
18 hemoglobin A<sub>1c</sub> -- was the same in these two groups.

19           So, then we dug down into the results  
20 from the Phase III studies and tried to identify  
21 those patients who had nocturnal hypoglycemia. Out  
22 of those who reported events, there was  
23 approximately 50 percent who also -- no, these are  
24 only the reported events. When we put them into the  
25 categories of either being from 6:00 pm to midnight

1 or midnight to 8:00 am, it became pretty clear that  
2 the dark blue one, which is the repaglinide, had  
3 more hypoglycemic events -- slightly more  
4 hypoglycemic events during the evening time, but a  
5 lot fewer hypoglycemic events during the nighttime.  
6 This is 4.5 percent and the difference was up to  
7 16.5 percent with the glyburide. So, this reflects  
8 very well the action profile of the drug and the  
9 clinical outcome of it, namely the glycemia.

10 We go to the next slide. We also looked  
11 into the patients who actually measured their blood  
12 glucose when they had a hypoglycemic event. As you  
13 can see here, it is divided into those who had a  
14 level which was less than a measured blood glucose  
15 less than 30, between 30 and 40, 40 and 50, 50 and  
16 60, and so forth. The blue, again, is the  
17 repaglinide patients. Those patients who then  
18 experienced a hypoglycemic event went and took a  
19 blood glucose measurement. You can see that the  
20 glyburide curve, which would be something like this  
21 -- there is a lot more reports on very low blood  
22 glucose values. The repaglinide curve is, so to  
23 speak, shifted to the right. This, again, is an  
24 indication that the drug has shorter action and  
25 furthermore, that it results in fewer low



1 the last slide here which says that "preprandial  
2 treatment with repaglinide leads to significant  
3 improved glycemic control, yet the risk of low blood  
4 glucose values and severe hypoglycemic events is  
5 low."

6 Thank you.

7 DR. CHEATHAM: Thank you, Dr. Damsbo.

8 If I could just bring the clinical  
9 dilemma now full circle, and Dr. Marcus, if I could  
10 just take your question at that point? Thank you.

11 So, now, we have a situation in which  
12 earlier diagnosis has been addressed at many levels.  
13 Of course, we now have had new guidelines  
14 established for the diagnosis of diabetes, hoping  
15 that by doing so we actually will shift the curve to  
16 a degree in regard to when diabetes is diagnosed.  
17 Greater sensitivities for the need of diagnosis and  
18 treatment is being accomplished through patient  
19 education and also recognition programs that are  
20 being administered, both by governmental agencies  
21 and also by professional organizations. But the  
22 search and continued improvement upon the idea of a  
23 potent and effective therapy with minimal impact on  
24 significant hypoglycemic events continues.

25 There's a suggestion, at least, by this

1 data that this particular agent, being one that does  
2 admittedly result in some degree of hypoglycemia,  
3 but it appears that when hypoglycemia occurs, it's a  
4 forgiving hypoglycemia. It may very well help to  
5 add to the armamentarium that we have. It's no  
6 doubt a potent drug. In dealing with primary  
7 failures and secondary failures? Well, that's  
8 another issue. We can't present any data today  
9 necessarily dealing with that, although the  
10 suggestions that you have been giving certainly  
11 would be ones that the company would be very  
12 interested in pursuing because there may be some  
13 observation there.

14 At the end of the day, our concern in  
15 diabetes as diabetologists is that we add to the  
16 armamentarium to give more effective therapy. That  
17 we're able to, even if it's bit by bit -- but in  
18 this situation, we believe as a company that we have  
19 an agent that expansively adds to the ability to  
20 treat individuals with type 2 diabetes with a potent  
21 drug with minimal risk of hypoglycemia, and  
22 hypoglycemia that when it occurs is minimal and  
23 individuals recover from it, at least presumably,  
24 without significant problems.

25 We also have anecdotal information. A

1 question was asked whether or not patients have  
2 concerns about having to take the medication three  
3 times a day. Through our studies, we do have  
4 anecdotal information that comes back from those  
5 individuals that tells us that they like the idea of  
6 designing their day and their meals to this  
7 particular dosing. That data has been collected and  
8 can be alluded to, although it's not as hard as the  
9 clinical research data that you have seen.

10 In regard to the scattergram that you  
11 saw in regard to responsiveness compared to the  
12 factor of dosing level, I think it's important to  
13 keep in mind that as I've pointed out, we deal with  
14 primary and secondary failures. Indeed, our patient  
15 populations for that particular slide in regard to  
16 responsiveness of glycemic control or change in  
17 glucose with increasing dosage was not specified for  
18 a distinct group of people. In diabetes, we deal  
19 with people who exist all along the continuum of  
20 beta cell responsiveness. The natural history of type  
21 2 diabetes is one in that the longer individuals  
22 have diabetes, the less responsive the beta cell  
23 becomes. So, when you add any one particular dose  
24 and use that in a broad population of patients,  
25 you're bound to see varying responsiveness if you

1 have not controlled for the duration of diabetes, or  
2 at least somehow predetermined the beta cell  
3 responsivity from the very beginning.

4           So, I think in addition to perhaps some  
5 of the other explanations in regard to protein  
6 binding and others, that also needs to be borne in  
7 mind in regard to the responsiveness from dose  
8 finding. And indeed, again, in type 2 diabetes with  
9 the use of oral sulfonylureas, we've trained to  
10 start with low doses and work our way up, titrating  
11 individuals patients to where we find the  
12 responsivity. Because this drug undoubtedly in low  
13 doses gives greater than 50 percent responsivity at  
14 low doses. What we reach for as we increase the  
15 dose beyond that are the few people that will  
16 respond to higher dosages because their beta cells  
17 perhaps, if you will accept a simplistic finical  
18 endocrinologist's suggestion, their beta cells need  
19 a little bit more kick in the butt in order to  
20 release, perhaps, a little bit more insulin. But  
21 that certainly isn't seen in the broad spectrum.

22           I'll stop here and answer questions.

23           Dr. Marcus?

24           DR. MARCUS: Yes. Thank you.

25           One of the worst examples of

1 hypoglycemia that most of us have seen I think is  
2 the patient who has come in with profound glycaemia  
3 because it has been mixed with an oral agent, or  
4 insulin has been mixed with alcohol. One would not  
5 predict, since this drug apparently does not inhibit  
6 gluconeogenesis, that that would be a particularly  
7 bad combination or at least it would be better with  
8 this drug than it would be with other oral agents.

9 Do you have any experimental evidence in  
10 your preclinical data to look at an interaction  
11 between alcohol or aspirin, for example, and this  
12 drug?

13 DR. CHEATHAM: I just looked back to my  
14 basic scientists and pharmacologists, but the answer  
15 is no. I am not aware of any and they tell me no.  
16 That certainly is very, very important and it again,  
17 becomes something that a drug of this type lends  
18 itself to study within.

19 DR. WHISNANT: But the clinical  
20 correlate, sir, is that we've had no reports of  
21 coma, loss of consciousness, hospitalizations, for  
22 that kind of problem. That's a serious kind of  
23 complication.

24 DR. MARCUS: Sure.

25 ACTING CHAIRMAN SHERWIN: José?

1 DR. CARA: Yes, you know, I need to  
2 reiterate the fact that a lot of the patients that  
3 you put in your trials were not in optimal control  
4 either at the beginning or at the end. My concern  
5 is that as you pushed the envelope, so to speak, the  
6 incidence of hypoglycemia may, in fact, increase.

7 Have you looked at patients, for  
8 example, with glycohemoglobins of less than seven-  
9 and-a-half? And looked at the incidence of  
10 hypoglycemia in those patients versus patients with  
11 higher glycohemoglobins, or at least done some sort  
12 of a scattergram where you look at incidents of  
13 hypoglycemia versus glycohemoglobin levels, for  
14 example? I'm sure you must have that data.

15 DR. CHEATHAM: Yes. Yes, indeed, we do  
16 have that data and I think Dr. Whisnant can speak to  
17 that data directly.

18 DR. WHISNANT: It's in that set  
19 somewhere. Keep going. Keep going.

20 There it is, Dr. Cara. I think I showed  
21 those two slides earlier in another context.

22 DR. CARA: But this is baseline  
23 glycohemoglobin.

24 DR. WHISNANT: That is correct. You  
25 want it at the time of the hypoglycemic episode?

1 ACTING CHAIRMAN SHERWIN: Yes, right.

2 DR. CARA: While on therapy.

3 DR. WHISNANT: I do not have that data.

4 We could do you an analysis of the nearest HbA<sub>1c</sub>  
5 proximate to the event, okay? It wouldn't be  
6 exactly at the time of.

7 DR. CARA: Sure. No, but, let me make  
8 sure I understand this slide correctly.

9 DR. WHISNANT: Okay.

10 DR. CARA: When you say baseline  
11 glycohemoglobin, it's glycohemoglobin before  
12 entering the study?

13 DR. WHISNANT: At the time of  
14 randomization.

15 DR. CARA: So, it doesn't tell you  
16 anything about the incidence of hypoglycemia while  
17 on study drug.

18 DR. WHISNANT: It only uses a baseline  
19 predictor. That's all it does. It tells the doctor  
20 if the patient starts out with this relative level  
21 of HbA<sub>1c</sub>, they are more or less likely to be one of  
22 those patients who will be trouble.

23 ACTING CHAIRMAN SHERWIN: Maria?

24 DR. NEW: I just want to comment that  
25 the changes in hemoglobin A<sub>1c</sub> from the beginning to

1 the end are not very great. Therefore, this  
2 probably does relate to your question. If somebody  
3 starts out with good control and a hemoglobin A<sub>1c</sub>  
4 below seven, do they have more or less hypoglycemia?  
5 That's your question. And since --

6 DR. CARA: No, my question is in the  
7 patient that is on therapy --

8 DR. NEW: But the changed the hemoglobin  
9 A<sub>1c</sub> --

10 DR. CARA: -- and responds with a  
11 glycohemoglobin level to where the glycohemoglobin  
12 gets more in a suitable target range of  
13 approximately seven-and-a-half or below, do they  
14 have a higher incidence of hypoglycemia?

15 DR. WHISNANT: What I can give you, Dr.  
16 Cara, after lunch is the delta HbA<sub>1c</sub> in each one of  
17 those subsets. Because we know as some measure of  
18 response within those subsets whether -- and in  
19 fact, it's pretty much as you would predict, as I  
20 recall the table. I don't have it on a slide. But  
21 as I recall the table, it's these higher dose  
22 patients with lower HbA<sub>1c</sub>'s -- and particularly in  
23 the next slide, please, -- the naive subset of  
24 patients who have relatively lower HbA<sub>1c</sub>'s. Those  
25 are the patients who need to be titrated. Those are

1 the patients where, you know, while we've subsetted  
2 down to a relatively small number of patients but  
3 still on a percentage basis, we're talking about,  
4 you know, a very substantial percentage of those  
5 patients need to be started on drug carefully at .5  
6 milligram where, in fact, a lot of those patients  
7 are going to respond.

8 DR. CHEATHAM: And I would just add to  
9 that that after over 1,200 patients being studied  
10 with this particular agent, we have absolutely no  
11 evidence of severe hypoglycemia with the use of this  
12 agent. Although that's just a statement. It's a  
13 statement from a clinical endocrinologist who would  
14 look at something like that and say "maybe that  
15 means something", and you experts, of course, would  
16 request the data to look at that question further.

17 ACTING CHAIRMAN SHERWIN: Yes, there  
18 have been no patients that have required assistance  
19 during all the trials?

20 DR. WHISNANT: That is correct.

21 DR. CHEATHAM: That is correct.

22 DR. NEW: And the overall change in  
23 hemoglobin A<sub>1c</sub>, if I took my notes correctly, is  
24 this 1.6 to 2.9 percent?

25 DR. WHISNANT: That is correct depending

1 on --

2 DR. NEW: That's from the beginning to  
3 the end of the study for all your patients?

4 DR. WHISNANT: Well, that's a range of  
5 delta HbA<sub>1c</sub>'s depending on the trial, depending on  
6 the subset of patients, depending on the dose. It's  
7 a total range. The least HbA<sub>1c</sub> delta that we saw  
8 was 1.6. As you would predict, that would be in  
9 previously treated patients, relatively resistant  
10 patients, patients, you know, with less  
11 responsiveness. The 2.9 number comes from the 065  
12 trial looking at naive patients only.

13 ACTING CHAIRMAN SHERWIN: Dr. Kreisberg?

14 DR. KREISBERG: I wonder, will you  
15 recommend this drug for all type 2 diabetic  
16 patients? Let me explain why I've asked that  
17 question.

18 DR. WHISNANT: Okay.

19 DR. KREISBERG: There seems to be an  
20 evolving concept, because of the continuum of type 2  
21 diabetes as already referred to, is that when  
22 patients are early in their disease or have  
23 relatively mild hyperglycemia, insulin deficiency is  
24 not the primary problem. It is only as they get  
25 further in their disease that that becomes a more



1 be looking at different ways of modulating therapy.  
2 I think the other tendency that's going on as  
3 opposed to the early disease, you know, "let's  
4 manage it. Prevent as much as possible." The other  
5 tendency that's going on in the community is the  
6 addition of one therapy to another. We understand  
7 that our drug, you know, is only one part of the  
8 armamentarium which primarily relates to providing  
9 insulin on a, hopefully, physiologic basis.

10 We have a study designed to compare this  
11 drug alone to a sensitizer alone, versus a  
12 combination. We've already shown you data that says  
13 that this drug can be added to metformin and do a  
14 pretty good job of salvaging metformin  
15 unsatisfactorily-treated patients. So, we're moving  
16 on to try to develop rational guidelines that will  
17 be consistent with exactly the direction that you're  
18 talking about.

19 Do we have data in glucose intolerant  
20 patients showing that you can modify the natural --  
21 we are not included in DPP. Wish we were because we  
22 think that's probably a logical kind of next step  
23 for understanding whether or not our drug and its  
24 not new mechanism, but very old mechanism -- I mean,  
25 you know, this is physiologic insulin, enhancement

1 of insulin. We believe that our drug has a chance  
2 of being effective in modulating the natural history  
3 conceivably, beta cell sparing, in this disease and  
4 we don't have those databases yet.

5 DR. CHEATHAM: Right. If I could just  
6 add on to that, Dr. Kreisberg? I think your  
7 question is extremely appropriate in this day and  
8 time.

9 There is no question, undoubtedly, type  
10 2 diabetes is a condition that usually coexists with  
11 insulin resistance and relative insulin deficiency.  
12 There are lots of clinical models, however, that  
13 would suggest that the insulin resistance itself  
14 although it may occur, does not become clinically  
15 apparent or at least does not cause clinical  
16 elevation of glucoses until there is relative  
17 decline in the ability of the beta cells to release  
18 insulin. I think the question still  
19 is, which avenue do we need to effect? If we take  
20 care of one particular side of the scale, what are  
21 we missing out on on the other side of the scale? I  
22 don't think there needs to be an argument back and  
23 forth in regard to whether we deal with insulin  
24 sensitizers or beta cell stimulators. The bottom  
25 line is that both of those defects exist in type 2

1 diabetes and present themselves as the clinical  
2 problem.

3           Additionally, we still know that most  
4 people with type 2 diabetes require some form of  
5 insulin augmentation in order to achieve optimum  
6 control. There is evidence that there is luring of  
7 hemoglobin A<sub>1c</sub>'s and people do better. But if we  
8 look at the broad spectrum of individuals who are  
9 treated with type 2 diabetes today, with all agents  
10 that are available, the vast majority of people  
11 still require some degree of insulin stimulation or  
12 insulin supplementation to achieve the guidelines  
13 that we're looking for.

14           DR. WHISNANT: Dr. Cara, an answer to an  
15 earlier question. It's an approximate answer if  
16 you'll allow that.

17           The difference in delta HbA<sub>1c</sub> in  
18 patients who have hypoglycemia versus those who do  
19 not have hypoglycemia is approximately a half-a-  
20 percent difference.

21           DR. CARA: So, what does that mean? The  
22 patients that dropped their glycohemoglobin more  
23 than half-a-percent have higher incidence of  
24 hypoglycemia?

25           DR. WHISNANT: No. It means that in

1 this analysis of the data, that patients who  
2 demonstrated hypoglycemia on average, have a better  
3 HbA<sub>1c</sub> response than those --

4 DR. CARA: Oh, by half-a-percent.

5 DR. WHISNANT: By half-a-percent than  
6 those who do not report hypoglycemia.

7 DR. CARA: And what sort of incidents  
8 are we talking about?

9 DR. WHISNANT: Well, the kinds of  
10 incidences that are on those --

11 DR. CARA: Okay.

12 DR. WHISNANT: For the population as a  
13 whole, the number to remember is a fourth to a fifth  
14 of the patients are going to have hypoglycemia. Why  
15 we've been through all this subsetting process is to  
16 try to identify the contaminating part of that  
17 number which is much higher, and therefore, requires  
18 special management. That's the goal of this  
19 subsetting process.

20 ACTING CHAIRMAN SHERWIN: I have a  
21 question about the meals, skipping lunch study.  
22 We're going to eat. I promise. Just a quicky.

23 First of all, the statement was six  
24 events occurred with glipizide or one of the other  
25 agents, or glyburide and none occurred. I didn't

1 know, first of all, what the n was overall.

2 Secondly, what's an event?

3 Third, my concern with that study is  
4 that the fasting glucose is about 15 to 20  
5 milligrams per deciliter lower in the comparator  
6 group. The level of glucose is about 15 to 20  
7 milligrams per deciliter lower in the comparator  
8 group during the interval with the meal that's  
9 skipped. Consequently, you could argue that results  
10 are very similar. So, you'd like to start them off  
11 at the same level of glucose if you're going to look  
12 at hypoglycemia in a well controlled population.

13 DR. DAMSBO: That's absolutely correct.  
14 It would have been ideal if they had started out at  
15 the same level, but this is, again, one of the  
16 defects. The comparison was to glyburide.

17 ACTING CHAIRMAN SHERWIN: My concern is  
18 -- I mean, obviously, this is the key element to the  
19 advantage. Not that the drug isn't efficacious, and  
20 the key study to show that really is hard to  
21 interpret.

22 DR. DAMSBO: It's hard to interpret from  
23 the point of view that they do not start out on the  
24 fasting blood glucose. I agree with you that makes  
25 it a little -- it confounds the whole thing a

1 little. But if you look at the actual profile and  
2 the curve is up there again now -- if you look at  
3 the actual profile and if you look at the increment  
4 at the breakfast meal -- that is, if you move the  
5 red curve up these 15 milligrams, right?

6 ACTING CHAIRMAN SHERWIN: Right.

7 DR. DAMSBO: You would have a higher  
8 increment, correct?

9 ACTING CHAIRMAN SHERWIN: Right.

10 DR. DAMSBO: And again, you will have a  
11 higher increment at the dinner time and you will  
12 have a lower value throughout the night.

13 So, we can not overcome. We can not do  
14 both. We can not have a short acting drug that, at  
15 the same time, lowers the fasting blood glucose to  
16 the level. It's very difficult. I would say that  
17 fasting blood glucose is one split second of the  
18 diabetic's life and does not really reflect the  
19 dynamics of the glucose and insulin curves of the  
20 patients.

21 ACTING CHAIRMAN SHERWIN: And the  
22 events? The event is level of glucose below a  
23 certain point or is it symptoms?

24 DR. DAMSBO: Yes. It was symptoms of  
25 which three of them were -- all of them were

1 biochemically measured because it was an in-house  
2 study. These events occurred, all of them, in the  
3 time period mentioned. Three of them were below 45  
4 milligrams. The rest of them were between 45  
5 milligrams and 55 milligrams.

6 DR. WHISNANT: Some below 45, some --

7 DR. DAMSBO: Yes.

8 DR. WHISNANT: This might help the  
9 perspective of the discussion a little bit in terms  
10 of the kinetic difference. Admittedly, this is not  
11 a dynamic study, Dr. Cara. This is a comparison of  
12 drug levels, drug profiles, if you will, for our  
13 drug versus two of the comparitors that we've  
14 studied.

15 Just as a point of reference, this is  
16 how those drugs look in terms oral dosing based upon  
17 the recommended dosing. Our drug would be given  
18 three-times-a-day with those three curves down  
19 there, and glyburide would be given once-a-day like  
20 that. Glipizide would be given like that. So,  
21 we're talking about a very substantial contrast in  
22 the kinetic profile of the different kinds of  
23 therapy. I think it is that contrast that Dr.  
24 Fleming is trying to get us to address in terms of  
25 the implications of what that means. Perhaps not so

1 much in terms of what happens at the time of our  
2 peak, but what happens between our peaks and at  
3 night.

4 ACTING CHAIRMAN SHERWIN: Do you know  
5 anything about the binding characteristics of the  
6 drug to the K channel? In other words, it's not  
7 just the drug level but how tightly the drug binds  
8 to its protein. Because if it stays on the  
9 molecule, it's going to have a longer duration of  
10 action.

11 So, my question is, how does the binding  
12 characteristics between this drug and the  
13 sulfonylureas -- are they the same at different  
14 sites, or obviously different -- or I think they're  
15 different. Presumably, that might affect how long  
16 the molecule stays on the protein.

17 DR. FUHLENDORFF: It's a very difficult  
18 question to answer because we tried to make the  
19 experiment and we couldn't keep it on the receptor.  
20 So, that was one thing. So that tells me, at least,  
21 that it's not a very long-lasting effect.

22 ACTING CHAIRMAN SHERWIN: That's  
23 helpful.

24 Are we ready to eat before we all get  
25 hypoglycemic?

1 MS. REEDY: There is a table reserved in  
2 Chatters for the Committee.

3 ACTING CHAIRMAN SHERWIN: Okay.

4 (Whereupon, the meeting was recessed at  
5 12:31 p.m., to reconvene later this same day.)

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1 company has done in its approach to develop this  
2 drug. We are basing our estimate of efficacy  
3 basically on three placebo controlled studies.  
4 That's to make a distinction between the placebo  
5 controlled studies and those that involved an active  
6 comparator. We can derive some interesting  
7 information from those one-year studies involving  
8 active controls, but they are not meant to, in  
9 themselves, demonstrate efficacy.

10 Now, we have the results of, for  
11 example, the next overhead from study 065. This is  
12 showing you the mean hemoglobin changes from  
13 baseline at each week visit. Then the study 033, I  
14 don't have an overhead for, but I think we should  
15 talk just a moment about the one imbalance that was  
16 seen in the patients entering the study. There was  
17 a greater preponderance of patients who were naive  
18 in the repaglinide group. I think, let's see, the  
19 comparison was 13 versus -- or let's see, 23 percent  
20 versus nine percent in the placebo group. That  
21 might tend to make the patients treated with  
22 repaglinide perform better. I think it would be  
23 useful if we looked at adjusted analysis where we  
24 look only at the patients who were not naive to  
25 therapy.

1 I wonder, Dr. Whisnant, if you could  
2 respond on that particular point?

3 DR. WHISNANT: I'm happy to.

4 If we could just replace the slide  
5 that's up with a slide from the projector?

6 Dr. Strange showed you this morning,  
7 ladies and gentlemen, this placebo controlled trial  
8 33. The slide that he showed you was a comparison  
9 of a two-to-one randomization for approximately 100  
10 patients randomized in this trial. This is the  
11 overall analysis that Dr. Fleming has referred to  
12 comparing the drug to placebo. Remember that this  
13 was a double-blind, placebo controlled, randomized  
14 assignment of patients. So, it's as controlled an  
15 observation as you can get. Whether you think that  
16 the increase in HbA<sub>1c</sub> for placebo controlled  
17 patients is as it should be, or is more than it  
18 should be or whatever, it is what it is. The delta  
19 between the two groups is as we reported, 1.8  
20 percent HbA<sub>1c</sub>.

21 The next slide shows the corrected  
22 analysis, if you will, adjusted analysis for this  
23 trial removing the naive patients. Sometimes  
24 randomizations are not balanced and in this  
25 particular case, the randomization came out to be 23

1 percent to nine percent, as Dr. Fleming has  
2 indicated. So, the red line indicates that for 26  
3 patients in the early phase, we ended up with 14  
4 patients up there who were in that naive removed  
5 analysis -- the analysis with this group of patients  
6 -- versus an end study of 43 patients in the treated  
7 patients. As you can see with this previously  
8 treated subset of patients, while this line doesn't  
9 drop quite as far as when you included the -- it  
10 turns out there were only three naive patients in  
11 that original subset, but the placebo patients still  
12 have their characteristic loss of glycemic control  
13 because they've been taken off of their therapy at  
14 the beginning of the trial.

15 So, our answer to the question,  
16 respectfully, is that we still have placebo control  
17 studies demonstrating efficacy.

18 DR. FLEMING: All right. We can  
19 certainly come back to placebo controlled trial  
20 evaluation at any point, but then we might go on if  
21 there are not questions about these particular  
22 studies offhand.

23 DR. NEW: I'm confused. The difference  
24 between the slide you showed before and this one is  
25 what, exactly?

1 DR. WHISNANT: Could we go back, please?

2 You'll notice that in the placebo group  
3 of patients, the red patients, that there were 29  
4 patients at baseline and 17 patients at the end of  
5 the trial.

6 DR. NEW: Right.

7 DR. WHISNANT: Next slide.

8 You'll notice in this analysis, there  
9 were 26 patients at baseline and 14 patients at the  
10 end of the trial. What that means is that we have  
11 removed from the analysis, those patients who had  
12 not been previously treated with OHA drugs. That  
13 is, those patients who are -- we've removed and what  
14 are remaining are the previously treated patients.  
15 The naive patients have been pulled out and we're  
16 left now with a comparison of patients who had been  
17 previously treated with oral hypoglycemic agents and  
18 are now taken off therapy for this trial.

19 DR. NEW: Okay. So here's my question  
20 then. You only took three patients out that were  
21 naive and the difference --

22 DR. WHISNANT: We took three patients --  
23 sorry.

24 DR. NEW: Then the difference in the  
25 treatment group -- never mind the placebo group --

1 is what?

2 DR. WHISNANT: We took three patients  
3 out of this group down here --

4 DR. NEW: Yes.

5 DR. WHISNANT: -- and we took 13  
6 patients out of that group up there because of the  
7 unequal randomization. Sorry, the other way around.

8 DR. NEW: So, the removal of 13 patients  
9 gave you such a profound difference in the response?

10 DR. WHISNANT: Well, actually, the delta  
11 for this subset analysis is in the same magnitude as  
12 the delta in the all-patient analysis. If you just  
13 flip back and forth between the two slides, you'll  
14 see that --

15 DR. NEW: The ordinate is changed?

16 DR. WHISNANT: Well, we're talking about  
17 a difference between 1.1 down to minus .6, which is  
18 about 1.8, right?

19 Next slide, we're talking about 1.7 down  
20 to about minus .1 which is 1.8. It's in a different  
21 position but the delta is the same.

22 DR. KREISBERG: But there must be a  
23 different significance. I mean, if you look at the  
24 treatment group, it's not different than zero. So,  
25 what you're basically saying now is that the drug

1 prevents any deterioration in glucose control,  
2 whereas before, with the other previous figure, it  
3 showed that there was actually a glucose lowering  
4 effect by lowering the hemoglobin A<sub>1c</sub> below the  
5 baseline.

6 DR. WHISNANT: We've actually shown that  
7 in several studies, Dr. Kreisberg. That's the  
8 nature of this beast that we're dealing with.

9 DR. KREISBERG: I understand that. But  
10 in this analysis, it basically shows no  
11 deterioration.

12 DR. WHISNANT: Well, it shows rather  
13 dramatic deterioration on placebo versus control of  
14 that deterioration --

15 DR. KREISBERG: Right.

16 DR. WHISNANT: -- right? So, whether  
17 you call that a maintenance effect or a therapeutic  
18 effect, it is still a difference between patients  
19 who are not receiving the drug. I think it's an  
20 important word "distinction". For relatively  
21 responsive naive patients, you see a much nicer  
22 reduction, or what you might call clinically a  
23 treatment, right, as opposed to for previously  
24 treated patients with higher HbA<sub>1c</sub>'s, you see more a  
25 control of or maintenance of the control. We've

1       seen that repeatedly, not just with this drug but  
2       with a whole variety of other drugs.

3                   DR. KREISBERG:   Right.  But because we  
4       treat patients and not groups of patients, the  
5       effect that a patient realizes from the drug is in  
6       their mind, and I think in the physician's mind,  
7       does their glucose concentration get better, not  
8       whether it stays the same?  Whether it actually gets  
9       better is an important distinction, even though I  
10      know the nature of the beast.

11                  DR. WHISNANT:  Their glucose  
12      concentrations actually get better than their  
13      overall hypoglycemic control improves.  Their delta  
14      glucose around mealtime is a measurable effect, even  
15      in previously treated patients.  So that, the short-  
16      term management on a day-to-day basis with this drug  
17      gives you a different feeling when you're on the  
18      drug.  Whereas, the long-term maintenance of  
19      glycemic control is obviously very different for  
20      these previously treated patients as opposed to good  
21      prognosis, highly responsive, naive patients.

22                  DR. KREISBERG:  Except that the  
23      objective of all therapy is to get the hemoglobin  
24      A<sub>1c</sub> as low as you possibly can without producing  
25      hypoglycemic symptoms.  So, whether it stays the

1 same is really not an important issue because the  
2 improvement in the patient has to be reflected in  
3 the hemoglobin A<sub>1c</sub> which reflects the mean glucose  
4 concentration. So, keeping it the same is not an  
5 advantage.

6 DR. MOLITCH: No, but it's just equally  
7 potent to the prior sulfonylurea that they were  
8 using. That's all.

9 DR. KREISBERG: Right.

10 DR. MOLITCH: That's all.

11 DR. CARA: So, does that mean that at  
12 time zero, these patients were on treatment?

13 DR. MOLITCH: It's a two week wash-out.  
14 That's all, isn't that correct?

15 DR. WHISNANT: Just a two week wash-out.

16 DR. MOLITCH: Which is really too short  
17 a wash-out period.

18 DR. CARA: And then they just stopped  
19 the ongoing therapy and their glycos went --

20 DR. WHISNANT: Right.

21 DR. CARA: Do you know what the blood  
22 glycos were at baseline?

23 DR. WHISNANT: 8.5 mean.

24 DR. CARA: Mean, for both? That's the  
25 mean for the whole group, right? The whole group.

1 DR. WHISNANT: What do you mean the  
2 whole group?

3 DR. CARA: Before randomization. If you  
4 look at all the patients together, they had a mean  
5 of 8.5. Then they're randomized so presumably, you  
6 get the same number. But in this case, we got an  
7 unequal randomization and that was the reason for  
8 asking for the repeat analysis.

9 DR. WHISNANT: We may be, respectfully,  
10 Dr. Kreisberg, back to your earlier question about  
11 how we see this drug. You know, for previously  
12 treated patients who need more therapy, then maybe  
13 they either need more of this drug or some other  
14 drug added to it. So, we're into, you know, future  
15 studies kinds of questions.

16 ACTING CHAIRMAN SHERWIN: Cathy?

17 DR. CRITCHLOW: Could I ask for an  
18 interpretation or just a further interpretation of  
19 figure 6.4 in our briefing document? Which is  
20 essentially the same phenomenon of Prandin versus  
21 the comparitors showing no decrease and, in fact,  
22 maybe slight increases in HbA<sub>1c</sub>. Page 40.

23 DR. FLEMING: Yes. That is actually on  
24 the next overhead.

25 Mike, if you can put that up?

1                   This sort of leads into that point. The  
2 same general idea that we are, if anything,  
3 deteriorating a little bit in control. Again, I  
4 think we have to acknowledge that the particular  
5 design of the study where the dose was fixed could  
6 explain part of the fact that the glycemc control  
7 actually did deteriorate over that period of time.  
8 But this is exactly what I wanted to bring up at  
9 this point.

10                   Perhaps, Dr. Whisnant, if you'd like to  
11 comment about why we have this result?

12                   DR. WHISNANT: Does this answer your  
13 question?

14                   DR. CRITCHLOW: Yes.

15                   DR. WHISNANT: I think we have this  
16 result because that's what we set out to show. Not  
17 to be clever about it, but let me, you know, really  
18 comment on that.

19                   If you look at the dotted line which is  
20 047 trial, for instance, this is a compilation of  
21 the European trials indicated down at the bottom of  
22 the slide. So, in effect, it represents 1,228  
23 repaglinide patients and half that many comparitor  
24 patients. So, if you look, for instance, at this  
25 group of patients, follow the dotted line, what you

1 see is the study effect within a month or two  
2 because when you take better care of patients, you  
3 know, their glycemic control gets better. This  
4 happens to be fasting plasma glucose so this is the  
5 ongoing monitoring of the study, monitoring of the  
6 patients.

7           So, their fasting plasma glucose gets a  
8 little better as you put them on study. Then  
9 gradually over time, this drifts either toward or  
10 slightly above the number that they started with.  
11 Whether it drifts above the number that they started  
12 with depends on -- just can I stop one second?

13           Wong Chin, is this the attrition  
14 adjusted data or is this all patients? This is all  
15 European trials?

16           Kristian, do you know? It's all?

17           This is not attrition adjusted data.  
18 So, what you're seeing is all the patients were  
19 evaluated at that point in time. So, part of what  
20 you're seeing here is a slightly different  
21 population of patients as we go forward, right, and  
22 part of what you're seeing is the natural history of  
23 this disease. If you take a group of patients who  
24 have a mean HbA<sub>1c</sub> of eight-and-a-half or nine and  
25 whose FBGs are not very well controlled, then their

1 natural history if you follow them -- well,  
2 certainly, their natural history if you follow them  
3 on placebo is that they go up like that. They go  
4 way up. That's the problem in doing placebo control  
5 trials, as you can imagine. But their natural  
6 history on any insulin or insulin-like, or insulin  
7 secretion therapy drifts just like that.

8 DR. CRITCHLOW: So, if a patient  
9 required insulin during the course of the trial, are  
10 they in the ones that are withdrawn due to  
11 inadequate --

12 DR. WHISNANT: They dropped out of the  
13 trial.

14 DR. CRITCHLOW: Okay.

15 DR. WHISNANT: And the dropout rate was  
16 on the order of 30 percent for both arms.

17 DR. KREISBERG: There's just a slight  
18 discrepancy in the slide. It says hemoglobin A<sub>1c</sub>,  
19 but you talk in terms of millimoles of glucose,  
20 right?

21 DR. WHISNANT: Sorry. Well, that's the  
22 wrong -- let's see.

23 DR. KREISBERG: They could be the same,  
24 actually.

25 DR. WHISNANT: This is fasting plasma

1 glucose. It's the wrong heading.

2 DR. KREISBERG: Okay.

3 DR. WHISNANT: Okay? I know that the  
4 mean HbA<sub>1c</sub> would be down there, right, nine -- a  
5 little more than nine. So, this is millimoles.

6 DR. MARCUS: Well, we're told that this  
7 is a problem with this being a fixed dose study, but  
8 how many of these patients or in how many of these  
9 studies was the dose fixed at four milligrams three  
10 times-a-day which meant that sure, it's fixed dose  
11 but you can't go higher? It's a max dose.

12 DR. WHISNANT: The answer is about half.  
13 About half the patients failed to achieve a  
14 satisfactory FBG at one of the lower doses and  
15 therefore, completed the titration scheme all the  
16 way to four milligrams.

17 DR. MARCUS: I wish I felt more  
18 comfortable with the assertion that this is the  
19 nature of the beast. I'm not a diabetologist, but I  
20 do see them in our clinic and I have to say we have  
21 people who maintain adequate hemoglobin A<sub>1c</sub>'s that  
22 is seven or below long-term without a sign of a  
23 drift. Now, I don't know. I'd like to get maybe  
24 Bob Sherwin or Kreisberg or someone has --

25 DR. HIRSCH: Let me just ask a question

1 before. Can you just help me to understand the  
2 slide that I'm looking at? I can't see that one,  
3 but this is page 40 which I think is the one that  
4 was referred to.

5 DR. MARCUS: Yes, that's it.

6 DR. HIRSCH: What that shows is that  
7 everybody on the drug seems to be getting a slow  
8 drift upward of  $A_{1c}$  hemoglobin as compared to the  
9 slide we saw before in which the treated group  
10 seemed to be drifting a little bit downward from a  
11 zero position. This is a percent change. I'm  
12 sorry, it must be a different study or something.  
13 I'm confounded now.

14 DR. FLEMING: You know, I think I am the  
15 culprit here in that I have taken the wrong figure,  
16 which may not actually be in your book, and put the  
17 right title over it. If you'll excuse me for that.

18 Can you pull up figure 64.

19 DR. HIRSCH: Is that the one that's on  
20 page 40?

21 ACTING CHAIRMAN SHERWIN: That's  
22 glycohemoglobins.

23 DR. FLEMING: Okay, well, it's the same  
24 thing.

25 DR. HIRSCH: There you go. But

1       whichever it is, I don't understand it. I mean, I  
2       see what it says, but I don't understand. The  
3       figure we saw before this five or ten minutes ago  
4       showed everybody sort of drifting downward in A<sub>1c</sub>  
5       hemoglobin.

6                 DR. WHISNANT: Over three months, sir.

7                 DR. HIRSCH: Over three months?

8                 DR. WHISNANT: Right.

9                 DR. HIRSCH: I see. So, in all  
10       instances if you keep it going a year, it looks like  
11       in this situation, you're worse off than when you  
12       started with A<sub>1c</sub> hemoglobin.

13                DR. WHISNANT: I'm sorry. We showed you  
14       two sets of data. The initial data that I showed  
15       you the corrected analysis for was the 33 data which  
16       was a 12 week study -- sorry, 16 week study.

17                DR. HIRSCH: So, this is the best one  
18       for time.

19                DR. WHISNANT: And that's the year data  
20       that you're looking at now. You see a couple of  
21       things from the slide that's in front of you.

22                DR. HIRSCH: Well, I can't. I mean, I  
23       apologize. You'll have to tell me because I can't  
24       see.

25                DR. WHISNANT: Okay, all right.

1 DR. HIRSCH: I'd have to look in the  
2 book because I can't see the slides at all. So, go  
3 ahead, just tell me about it and I'll try to  
4 understand it. They're invisible to me.

5 DR. WHISNANT: Okay. From the slide  
6 that's in your book --

7 DR. HIRSCH: Good, page 40.

8 DR. WHISNANT: It's also the slide  
9 that's in front of the group.

10 DR. HIRSCH: Good.

11 DR. WHISNANT: The top line you see is  
12 the US trial, the little dotted line up on top?

13 DR. HIRSCH: Yes.

14 DR. WHISNANT: What that shows is that  
15 in the United States, we start with a patient  
16 population that's in relatively poor control. Their  
17 HbA<sub>1c</sub>'s are approaching nine. As Dr. Cheatham  
18 showed you before lunch, that's where we are in this  
19 country with treating type 2 diabetes.

20 DR. CRITCHLOW: Excuse me. These are  
21 all repaglinide treated patients, everybody on this  
22 slide?

23 DR. WHISNANT: Those are repaglinide  
24 treated patients. That is correct.

25 DR. CRITCHLOW: What I didn't understand

1 when I originally asked the question was, it said  
2 something to the effect of differences between that  
3 and the comparator. So, maybe you could just  
4 explain what -- so this is just over time, the HbA<sub>1c</sub>  
5 levels?

6 DR. WHISNANT: This is HbA<sub>1c</sub> for each of  
7 the five trials and the European patients tend to be  
8 better taken care of or better treated or whatever,  
9 or they don't eat as much or whatever.

10 DR. CRITCHLOW: Then what is going on  
11 with the patients in the comparator arms?

12 DR. WHISNANT: The same.

13 DR. HIRSCH: All we see here are the  
14 repaglinide, is that correct?

15 DR. WHISNANT: It's the same.

16 Give me primary 49 because the lines are  
17 right on top of each other. On a per study basis,  
18 the lines are right on top of each other, yes, sir.

19 DR. ILLINGWORTH: Do you have data on  
20 the same slide of body weight? Did this  
21 progressively increase?

22 DR. WHISNANT: I commented on body  
23 weight in the comparator trials this morning. For  
24 the repaglinide patients in the comparator trials,  
25 on average, it's about half-a-kilo weight loss over

1 the year versus the comparator. For some studies,  
2 for some comparitors, it's a kilo of weight gain;  
3 for others, it's half a kilo weight loss. So, it's  
4 in the same order of magnitude.

5 Why did you ask the question?

6 DR. ILLINGWORTH: It's a confounding  
7 variable if the glyceemic control varies.

8 DR. WHISNANT: Yes, okay. I did not do  
9 a covariant on weight for glyceemic control.

10 There's the two drugs. At least in the  
11 US trial, the repaglinide -- and here, again, is  
12 that three month study effect. Then gradually, over  
13 time, they go back to about where they started. I'm  
14 reminded that there's a number of natural history  
15 studies that some of us in the room are aware of  
16 that show the deterioration is on the order of a few  
17 tenths of an HbA<sub>1c</sub> percent per year in natural  
18 history studies that have been done, including  
19 UKPDS, et cetera.

20 DR. ILLINGWORTH: One other question  
21 related to that issue is do you have data on  
22 compliance to the drugs where the patient is more  
23 compliant in the first three months and then became  
24 more complacent as they were on therapy longer,  
25 based on pill counts or --

1 DR. WHISNANT: The compliance rate  
2 overall was a number that Poul gave me this morning,  
3 80-some percent --

4 DR. STRANGE: In the 49 trial, 93  
5 percent of the patients took at least 80 percent of  
6 the drug.

7 DR. WHISNANT: Eighty percent of the  
8 drug was taken by 93 percent of patients overall,  
9 but that's not the question you're asking. You want  
10 it by month or something on that order?

11 DR. ILLINGWORTH: By time, yes.

12 DR. WHISNANT: We don't have it here,  
13 but we can go into a database and look it up.

14 DR. ILLINGWORTH: Because that may  
15 explain some of your variations in control.

16 DR. WHISNANT: It's worth looking at.

17 DR. KREISBERG: Dr. Whisnant?

18 DR. WHISNANT: Sir?

19 DR. KREISBERG: You have similar type of  
20 data on your patients who were naive. I believe  
21 that they lost --

22 DR. WHISNANT: Yes, sir.

23 DR. KREISBERG: -- their hemoglobin A<sub>1c</sub>  
24 dropped by over two percent. Do I recall that  
25 right?

1 DR. WHISNANT: The largest decrement was  
2 2.9 percent in a naive subset in protocol 65.

3 DR. KREISBERG: Do we have a follow-up  
4 of them over a 12 month period of time?

5 DR. WHISNANT: Yes, sir. We have a  
6 slide, right, for the naive subset in 49? We have  
7 six month data, but we don't have the 12 month data.

8 In the six month trial, I think actually  
9 we showed you that subset --

10 DR. KREISBERG: You may have.

11 DR. WHISNANT: -- analysis this morning.  
12 What happens is that the naive subset of patients  
13 get a nice what you would call "therapeutic  
14 response." Their HbA<sub>1c</sub>'s go down over three to six  
15 months. Then if you follow that naive subset over  
16 the subsequent year, then they drift to about half  
17 as high as they were. They lose about half of what  
18 you gained when you were starting them on therapy.  
19 I believe that is also -- sorry, this is not an  
20 excuse. It is my perception that that is the  
21 general experience with, if you'd want to call it  
22 the natural history. But that's the general  
23 therapeutic experience with these kinds of drugs.

24 DR. FLEMING: Well, just summarizing, we  
25 can see that there is a subacute effect on the order

1 of 1.6 or more percent hemoglobin units. But  
2 depending on the patient population, this can be  
3 considerably less, particularly over a period of  
4 time. We do not have a study that formally  
5 demonstrates durability, though these active  
6 comparator studies at least give us a look at a  
7 single fixed dose over a one-year period of time.

8 I wonder if there are any other points  
9 to be made about efficacy before we move on?

10 DR. HIRSCH: Yes, I had -- I wonder if  
11 you or any member of the industrial group could just  
12 succinctly give me the best evidence for a  
13 difference in hypoglycemia. I'm confounded now by  
14 all the different kinds of things that are going on.  
15 But what's the single best piece of information that  
16 with this drug, there's going to be less  
17 hypoglycemia in one year than with any other drug?

18 DR. WHISNANT: Meaningful hypoglycemia  
19 difference, I believe is best demonstrated by  
20 patients who have meaningful hypoglycemia. What  
21 we've shown is that there's one-third -- one-half to  
22 one-third depending on the trial as many patients  
23 discontinue therapy for reasons of hypoglycemia,  
24 number one. We've shown that in the repaglinide  
25 treated patients versus glyburide treated patients

1 in long-term treatment trials, that one-fourth as  
2 many patients have blood glucoses lower than 45.  
3 We've also shown that there were no serious events,  
4 including hospitalizations and coma, with our drug  
5 compared to a countable number, not a statistical,  
6 you know, huge number with the comparator drug.

7 So, we would --

8 ACTING CHAIRMAN SHERWIN: What is the  
9 countable number? Because you haven't given us a  
10 countable number.

11 DR. WHISNANT: It's a few. I don't  
12 remember.

13 DR. HIRSCH: The one-fourth who were  
14 lower than 45 -- there was a ratio of one to four  
15 you said.

16 DR. WHISNANT: One to four.

17 DR. HIRSCH: Okay, and the total number  
18 that we're talking about who would achieve this less  
19 than 45 -- how many?

20 DR. WHISNANT: Eight percent of 1,200  
21 versus 33 percent of --

22 DR. HIRSCH: Eight percent versus --

23 DR. WHISNANT: No, sorry, that's not  
24 quite right. It's eight percent of those who had  
25 BGM measurements which is 50 percent of the 1,228

1 people had BGM -- 50 percent of people with  
2 hypoglycemia reported BGM measurements. Of those,  
3 eight percent of those versus 33 percent of those  
4 had blood glucoses lower than 45.

5 DR. HIRSCH: Oh, so it's eight percent,  
6 33 percent versus what percent?

7 ACTING CHAIRMAN SHERWIN: Could you get  
8 that table up? Maybe that would help us a little  
9 bit?

10 DR. WHISNANT: You want to see that  
11 table again?

12 ACTING CHAIRMAN SHERWIN: Yes. We have  
13 many times, but --

14 DR. WHISNANT: Okay.

15 ACTING CHAIRMAN SHERWIN: The other  
16 point, you know, regarding these issues is I haven't  
17 heard anything about statistics throughout. I mean,  
18 had there been a statistical analyses done by the  
19 FDA of these data in terms of --

20 DR. FLEMING: We certainly have examined  
21 the efficacy data formally, but we've not applied a  
22 biostatistical analysis of the safety data as of  
23 yet.

24 ACTING CHAIRMAN SHERWIN: Yes, because I  
25 think that's critical in terms of actual, you know,

1 what we're saying here. I mean, clearly, we need to  
2 know what's statistically significant and what  
3 isn't.

4 DR. WHISNANT: Dr. Sherwin, here's some  
5 hypoglycemia for you. This is the elderly subset of  
6 patients, okay? The subset where it's clinically  
7 more of a problem, if you will. Of 343 patients  
8 exposed, 16 percent had hypoglycemia and one-and-a-  
9 half percent discontinued for reasons of  
10 hypoglycemia. One-and-a-half percent of 343 as  
11 opposed to 4.6 percent of 131.

12 DR. HIRSCH: As opposed to, let's see --  
13 16 percent as opposed to --

14 DR. WHISNANT: Sixteen percent of total  
15 versus 18 percent of total.

16 DR. HIRSCH: So, they had the same  
17 amount or whatever, the same reported hypoglycemia  
18 in the two groups.

19 DR. WHISNANT: These two numbers are  
20 probably not different.

21 DR. HIRSCH: Okay.

22 DR. WHISNANT: These two numbers  
23 probably are different. Okay?

24 Of the patients with hypoglycemia, 45  
25 percent of them had meter readings. Eight percent

1 of the meter readings were below 45 milligrams  
2 percent as opposed to 33 percent of the 63 percent  
3 who had meter readings in the glyburide treated  
4 patients.

5 Now, let me hasten to add --

6 ACTING CHAIRMAN SHERWIN: This is very -  
7 - I must say it's very confusing to sort out actual  
8 numbers.

9 DR. HIRSCH: It's even worse if you have  
10 to look around this way.

11 ACTING CHAIRMAN SHERWIN: Yes, Jules,  
12 would you like to -- I mean, we could put it --

13 DR. NEW: Jules, you can put a chair  
14 here.

15 ACTING CHAIRMAN SHERWIN: Yes. I  
16 apologize for the room. I don't think the  
17 government could afford a larger room.

18 DR. WHISNANT: Sixteen percent of 343  
19 reported hypoglycemias.

20 ACTING CHAIRMAN SHERWIN: So, it's like  
21 60 patients or something like that. Less than 60.  
22 About 50 something.

23 DR. WHISNANT: Forty-five percent of  
24 those had blood glucose monitoring.

25 ACTING CHAIRMAN SHERWIN: So, it's about

1 25 patients.

2 DR. WHISNANT: Eight percent of the 25  
3 reported very low blood glucoses.

4 ACTING CHAIRMAN SHERWIN: It's about  
5 three patients.

6 DR. WHISNANT: Eighteen percent of 131  
7 patients reported hypoglycemia. 4.6 percent of 131  
8 discontinued for reasons of hypoglycemia.

9 ACTING CHAIRMAN SHERWIN: So, it looks  
10 like about four or five patients in the glyburide  
11 group versus three patients in the --

12 DR. MARCUS: It's about three versus  
13 seven.

14 ACTING CHAIRMAN SHERWIN: Are you sure?

15 DR. MARCUS: Well, 131 -- it's about one  
16 out of five --

17 ACTING CHAIRMAN SHERWIN: That's about  
18 25 or so.

19 DR. MARCUS: Okay, yes.

20 ACTING CHAIRMAN SHERWIN: Twenty-five,  
21 so it's about 15 and a third of those is five.  
22 That's what I'm saying. So, I think it's three  
23 versus five, with the caveat that you have twice as  
24 many --

25 DR. WHISNANT: Three versus 15 then.

1       There are three times as many patients.

2                   DR. MOLITCH:   Somehow, it would seem  
3       that this is one of the major reasons why this drug  
4       is being brought forth to us to look at on an  
5       accelerated fashion, that some sort of statistics  
6       would have been done on this data to see if these  
7       are either clinically meaningful or statistically  
8       meaningful?  You know, we need some help with this  
9       and why wasn't it done, if that's the reason it's  
10      being brought forward?

11                  DR. FLEMING:   Well, I actually felt that  
12      we did not have much of a signal for a difference.  
13      That these results did not make the case that there  
14      was a major difference in outcome.  So, my position  
15      has been that theoretically, the drug offers this  
16      potential, but it has not been conclusively  
17      demonstrated.  We have some signals here, but I'm  
18      not sure that they would convince anybody.

19                  DR. WHISNANT:   And we would hasten to  
20      add that there's been no purpose designed  
21      hypoglycemia study.  We're talking about monitoring  
22      of adverse events out of efficacy trials.

23                  ACTING CHAIRMAN SHERWIN:  Right.

24                  DR. WHISNANT:   So, unless you've done a  
25      trial which we actually have designed now to look at

1 hypoglycemia in the elderly, where every patient has  
2 been monitored preferably under observation like in  
3 a retirement home, nursing home community, et  
4 cetera, then there's no purpose designed study where  
5 analyses of this kind of magnitude of change are  
6 appropriate. So, we're reporting what we're  
7 reporting when you look at the absence of serious  
8 events, the absence of severe events, a lower  
9 frequency of discontinuation of events, a lower  
10 number of patients who reported nighttime events.

11 Out of those who were monitoring their  
12 blood glucose and out of those who were reporting,  
13 the profile is consistent with the theoretical  
14 advantages of this drug. We are committed to do --  
15 actually, already planning -- a purpose design study  
16 to look at hypoglycemia including quality of life,  
17 et cetera.

18 ACTING CHAIRMAN SHERWIN: José?

19 DR. CARA: I get the gist that based on  
20 your focus on the comparator studies this morning,  
21 and yet Dr. Fleming's comments that they're going to  
22 look strictly at the placebo controlled studies,  
23 that there's some miscommunication here in terms of  
24 the data that we should be looking at. Is that, in  
25 fact, the case?

1 DR. WHISNANT: No miscommunication at  
2 all except, perhaps, what we've miscommunicated to  
3 you. Let me clarify specifically.

4 The substantial evidence required for  
5 the demonstration of efficacy is two adequate and  
6 well controlled trials. The best adequate and well  
7 controlled trial design is a placebo controlled,  
8 double blind trial and we've done three of those.  
9 So, we believe that the efficacy of this drug in  
10 type 2 diabetes has been unequivocally demonstrated.

11 On the other hand, the other part of the  
12 equation is the safety part of the equation and the  
13 numbers of patients and the durations of trials done  
14 in placebo control trials does not allow us an  
15 adequate full evaluation of the safety profile of  
16 the drug. Therefore, the company carried out five  
17 relatively large comparator studies, four of them in  
18 Europe where you can't do placebo control trials.  
19 It is that safety database that Dr. Edwards  
20 concentrated on primarily this morning.

21 DR. CARA: Okay. Let me ask you this.  
22 I was quite intrigued, surprised and concerned,  
23 about what happens to the data when you take out the  
24 naive patients. In your comparator studies, what  
25 was the percent of naive patients there?

1 DR. WHISNANT: Twelve to 15 percent per  
2 trial.

3 DR. CARA: And what happens to the data  
4 when you take out naive patients?

5 DR. WHISNANT: You get the same  
6 equivalence when you used all patients. It's a  
7 subset. It's a minor subset.

8 ACTING CHAIRMAN SHERWIN: Dr. Marcus?

9 DR. MARCUS: We are on the subject of  
10 efficacy and I expressed an opinion earlier in this  
11 proceeding that I think efficacy includes a variety  
12 of other endpoints. We were going to be shown the  
13 results of those. I think we can't leave this topic  
14 without having the company have an opportunity to  
15 show us those endpoints.

16 DR. WHISNANT: Would you like to see the  
17 lipid data?

18 DR. MARCUS: Absolutely.

19 DR. HIRSCH: While they're doing that  
20 though, I did want to clarify my confusion which I  
21 think has been straightened out now. I  
22 misinterpreted efficacy to mean that this was a drug  
23 that was going to be efficacious in the prevention  
24 of hypoglycemia, which was sort of the thrust of my  
25 thinking about it this morning. Obviously, it was

1 an unfair thing on my part.

2 I've been convinced, I think, about the  
3 efficacy in terms of comparison as a hypoglycemic  
4 agent with other available oral agents, but we seem  
5 to be a little at sea. Although theoretically, it  
6 might be a good thing for spontaneous or other  
7 hypoglycemia. We don't have evidence at hand.

8 Am I now straightened out?

9 DR. FLEMING: I may have contributed to  
10 that confusion by saying that the attractive feature  
11 was the potential for reducing hypoglycemia.  
12 Certainly the company is not making a claim about  
13 reducing hypoglycemia.

14 DR. CARA: So, your primary endpoint, in  
15 other words, is still efficacy in terms of blood  
16 glucose and glycohemoglobin?

17 DR. FLEMING: That's right.

18 DR. EDWARDS: We said before lunch that  
19 we'd try and respond to the questions about the  
20 lipid profile with some data. I'm not sure whether  
21 I misunderstood the question before lunch or not. I  
22 believe I gave an accurate answer and we've tried to  
23 scramble together some actual results to show you.  
24 We don't have complete data on every trial, but  
25 we've got what we've got.

1           The data shown here is from the placebo  
2           controlled United States' study 065 in which  
3           repaglinide one milligram, repaglinide four  
4           milligrams, and placebo were compared. I've simply  
5           tried to show you on this slide what the baseline  
6           values for the cholesterol were in terms of mean and  
7           standard deviations and those at the end of the  
8           trial, in this case six months. As I tried to  
9           explain this morning, we do not believe they show  
10          any differences.

11                 In terms of triglyceride values, same  
12          presentation: number of patients, mean and standard  
13          deviation, the end of trial. The only thing you may  
14          be able to see -- and I haven't brought all the  
15          statistical analysis with us -- is that if you look  
16          at the triglyceride values, you can see some  
17          tendency perhaps in the higher dose group, but the  
18          standard deviation is so broad that you're not  
19          likely to be able to distinguish it.

20                 DR. MARCUS: Well, did you put that on a  
21          repeated measures -- that could easily be  
22          statistically significant.

23                 DR. EDWARDS: We have --

24                 DR. MARCUS: Or even just a paired to  
25          aspect. It's about a reduction of ten percent or

1       thereabouts and that could certainly --

2                   DR. EDWARDS:   Okay.

3                   Wong Chin, can you help me with that?

4                   DR. EDWARDS:   Okay.   Our statistician  
5       says we didn't analyze it.

6                   Okay, if we look at the long-term active  
7       control trials, the answer I tried to give this  
8       morning was that we did not see any difference when  
9       we compared repaglinide with sulfonylurea agents.  
10      What this data shows you, expressed slightly  
11      differently, the number of patients, the mean and  
12      the standard deviations, and the change from  
13      baseline to the last visit which in this case is a  
14      year study, and the confidence intervals around  
15      those changes.

16                  DR. CARA:   Do the asterisks mean  
17      significance?

18                  DR. EDWARDS:   Yes, they do.

19                  DR. KREISBERG:   What kind of units are  
20      you using there?   221 is a milligram per deciliter  
21      unit and then your change from baseline is 0.16 and  
22      0.20.   That must be millimolar.

23                  DR. EDWARDS:   I beg your pardon.

24                  DR. MARCUS:   Yes, the top label says  
25      millimoles per liter.

1 DR. EDWARDS: Okay.

2 DR. MARCUS: But it's a significant  
3 drop.

4 DR. EDWARDS: There was a significant  
5 drop, yes.

6 In those groups, same thing.

7 AA: So, the mean values are in  
8 millimoles -- or the changes are millimoles per  
9 liter and the baseline mean guides are going back to  
10 the deciliters?

11 DR. MARCUS: Now, these are fasting  
12 triglycerides, presumably. Overnight fasting?

13 DR. EDWARDS: Yes, these are fasting.

14 DR. MARCUS: Given what I think we've  
15 learned in the last few years about the potential  
16 importance of meal induced glypenia, if you were to  
17 follow-up these data -- which I think you need to  
18 do, follow up this whole area of concern -- it would  
19 be important to do more than just fasting TGs and  
20 cholesterol fractions, but to actually look -- I'm  
21 not sure when, but at some point, after meals in the  
22 immediate post-Prandial --

23 DR. EDWARDS: Thank you. We have  
24 planned to do exactly the study you describe because  
25 we hope that the prompt reduction of blood sugar

1 after meals seen with Prandin may hope to control  
2 post-prandial hypolipidemia. So, we have plans to  
3 do exactly what you describe.

4 DR. KREISBERG: The change that you show  
5 there for triglyceride is generously .1 millimolar  
6 which is about nine milligrams per deciliter, from a  
7 baseline of 220 with a standard deviation of 200. I  
8 would personally be shocked if that was  
9 statistically significant. But what I'd like to  
10 suggest to you is --

11 DR. MARCUS: It's not.

12 DR. KREISBERG: Oh, it's not. I thought  
13 there was an asterisk. Oh, that was the cholesterol  
14 that had the asterisk.

15 DR. EDWARDS: No, it's just a spot on  
16 the slide, I'm afraid.

17 DR. KREISBERG: You ought to also  
18 analyze your data, vis-a-vis the response in  
19 glycemc control. Because if you give a drug and  
20 there's no glycemc control, I personally would  
21 doubt that there would be any improvement in the  
22 triglyceride. If there is glycemc control, then  
23 you might reasonably expect there to be a  
24 relationship.

25 So, it may be that within this, you have

1 a subgroup that would actually show some improvement  
2 in the dyslipidemia that is shown in these types of  
3 patients, but it would have to be correlated with  
4 the improvement in glycemic control.

5 DR. EDWARDS: I understand your  
6 question. I'm not sure I can answer it, spot on.  
7 We thought you might go in that general direction,  
8 and so what we've got here from the integrated  
9 summary of the long-term trials, integrated summary  
10 of efficacy, is the change in baseline in HbA<sub>1c</sub> seen  
11 on the point patient-by-patient basis. Females  
12 shown in the circle, males shown in the crosses  
13 showing the change from baseline in the total  
14 cholesterol. We really don't feel that it shows  
15 anything.

16 Now, I was also asked did we have any  
17 other information about cardiovascular type risk  
18 factors. We don't have -- we have some very simple  
19 information on fibrinogen we've been able to gather  
20 over lunch. Again, just a very simple presentation  
21 of it. This is the data from the USA long-term  
22 active comparator trial, repaglinide/glyburide, with  
23 mean and standard deviations for fibrinogen at the  
24 beginning and the end of the trial. We don't  
25 believe they show any differences.

1 ACTING CHAIRMAN SHERWIN: Mark?

2 DR. MOLITCH: Now, I presume since you  
3 didn't show it, that we don't have any data on HDL  
4 and LDL? In these -- I know, for example, metformin  
5 will raise HDL, lower LDL, and the total cholesterol  
6 stays about the same.

7 DR. EDWARDS: The same trial repaglinide  
8 versus -- again change from baseline very small, so  
9 we don't believe there's any differences, but yes,  
10 we --

11 DR. CARA: Do you have the information  
12 regarding the percent of patients that did not  
13 respond to therapy, percent non-responders?

14 DR. WHISNANT: We know the percent of  
15 patients who did not achieve a FPG target in the  
16 comparator trials and that's about 43.

17 DR. CARA: Total patients?

18 DR. WHISNANT: Yes, who do not achieve  
19 the target in the titration period.

20 DR. CARA: And that's at the highest  
21 dose, four milligrams?

22 DR. WHISNANT: They're titrated all the  
23 way and they still don't achieve the target.

24 DR. CARA: And what percent is that of  
25 the total patient base?

1 DR. WHISNANT: It's about 43 percent.

2 DR. CARA: Oh, so it's not 43 patients.

3 It's about 43 percent.

4 DR. WHISNANT: Oh, yes.

5 DR. CARA: So, 43 percent --

6 DR. WHISNANT: You're targeting to 140.

7 DR. CARA: So wait a minute. Forty-

8 three of patients treated with Prandin did not

9 achieve a target blood sugar of --

10 DR. WHISNANT: 140.

11 DR. CARA: -- 140.

12 DR. MOLITCH: But that doesn't mean non-

13 responder.

14 DR. CARA: I'm sorry?

15 DR. MOLITCH: They can go from 280 to

16 180 and still not meet the target, but be a

17 responder.

18 DR. CARA: Well, the way that you  
19 defined responder was based on glycohemoglobin

20 level. Do you have that?

21 DR. MOLITCH: I just said it was  
22 something, maybe half-a-percent.

23 DR. CARA: Half-a-percent.

24 DR. MOLITCH: Or something like that.

25 DR. CARA: I mean, that's something

1 that's reasonable.

2 DR. MOLITCH: Actually, if we look at a  
3 year's worth of data -- if you're looking at an  
4 improvement of a half percent.

5 DR. CARA: If you exclude the naive  
6 patients --

7 DR. MOLITCH: -- talking about naive  
8 patients.

9 If you look at naive patients, how many  
10 have the half percent -- response?

11 DR. WHISNANT: A half percent of HbA<sub>1c</sub>,  
12 is that what you're asking?

13 DR. MOLITCH: Or greater.

14 DR. WHISNANT: Or less.

15 DR. MOLITCH: Whichever way you look at  
16 it.

17 DR. WHISNANT: Right. The percent  
18 responders defined by greater than .5 percent HbA<sub>1c</sub>,  
19 for instance, in the 24 week trial, placebo control  
20 trial.

21 DR. MOLITCH: Naive patients.

22 DR. WHISNANT: Right. For patients who  
23 started out greater than ten, then you get between  
24 67 and 72 percent of those having more than a half a  
25 point decrease. For patients who started out

1 between seven and eight, then the half-a-point  
2 decrease is obviously harder to achieve because  
3 you've only got between 38 and 52 percent of those.

4 DR. CARA: Thirty-eight to 52 percent?

5 DR. WHISNANT: Right.

6 DR. CARA: And how about in-between  
7 eight to ten, thereabouts?

8 DR. WHISNANT: In-between.

9 DR. CARA: Fifty-two to 67, somewhere  
10 around there?

11 DR. WHISNANT: Between the numbers,  
12 right.

13 So, using .5 as a reasonable measure of  
14 some value achieved, then you're talking about two-  
15 thirds of patients at high baselines and a third of  
16 patients at --

17 DR. CARA: And this was, again,  
18 titrating up to a maximum dose of four --

19 DR. WHISNANT: No, these were fixed dose  
20 trials.

21 DR. CARA: Oh, these were the fixed dose  
22 trials.

23 DR. WHISNANT: This was a comparison of  
24 one, versus four, versus placebo.

25 DR. CARA: Okay.

1 DR. WHISNANT: That's the best data we  
2 have.

3 DR. CARA: Okay, that's the best data  
4 you've got so you can't really separate out based on  
5 the dose?

6 DR. WHISNANT: Well, in the titration  
7 trials, I mean, you have all those confounding  
8 variables.

9 DR. CARA: Right.

10 DR. WHISNANT: So, it's harder to answer  
11 your question with any reasonable certainty using  
12 the titration format. Now, if you require a greater  
13 than one point decrement, then you get 50 to 64  
14 percent of patients at high baselines and only 28  
15 percent patients at low baselines. So, it's in that  
16 range.

17 ACTING CHAIRMAN SHERWIN: Dr. Marcus?

18 DR. MARCUS: Was there any change in  
19 average systolic or diastolic blood pressure or  
20 resting pulse rate?

21 DR. WHISNANT: On average, all the blood  
22 pressures that we have showed no changes, right?

23 DR. STRANGE: That's correct.

24 ACTING CHAIRMAN SHERWIN: Okay. I think  
25 we can go on to the next question.

1 Dr. Fleming, do you have any --

2 DR. FLEMING: No, I think that will do  
3 it.

4 ACTING CHAIRMAN SHERWIN: José?

5 DR. CARA: I'm sorry, just one last  
6 question. Was there any specific characteristic  
7 that you could kind of pinpoint or did you look at  
8 anything that would tell you which patients were  
9 likely to be responders versus non-responders based  
10 on the glycohemoglobin criteria? For example,  
11 degree of obesity, length of time of diabetes, age,  
12 et cetera, et cetera.

13 DR. WHISNANT: Right. I mean, there was  
14 an effort to determine correlates of response, the  
15 response rates by age -- greater than 65, less than  
16 65 are the same. There's a considerably higher  
17 response rate in naive patients than in previously  
18 treated patients. That's a song I've been singing  
19 all day. The final HbA<sub>1c</sub> is governed by the initial  
20 HbA<sub>1c</sub>, but the delta HbA<sub>1c</sub> is only to the extent that  
21 I've described for you, governed by the previous  
22 HbA<sub>1c</sub>. The response is not governed by C peptides.  
23 What else did we look at? Duration of  
24 treatment.

25 DR. HIRSCH: I just want to make sure I

1 understand the efficacy finally. You're saying, in  
2 fact, if we treated a lot of people now at the four  
3 milligram level, it would do all of the same things  
4 in terms of sugar lowering as glyburide or other  
5 oral agents do. But still 46 percent or thereabouts  
6 of the patients would still be sub-optimal in  
7 treatment, is that correct? Or not achieve the  
8 ideal goals? I mean, can we expect that half the  
9 people would not be as well treated as we might like  
10 after one year of this? Is that right?

11 DR. WHISNANT: That is the correct  
12 conclusion within the limits of the design and  
13 conduct of this trial. Obviously, if you want to  
14 optimize therapy of type 2 diabetes, you have to do  
15 a lot of things, perhaps including adding other  
16 drugs.

17 DR. HIRSCH: Or increasing the doses.

18 DR. WHISNANT: Or increasing the doses.

19 DR. HIRSCH: Which brings us to the next  
20 point, I guess.

21 DR. WHISNANT: Right.

22 DR. MOLITCH: But Jules, that's also  
23 their target of 140 and optimally, we might want to  
24 be even considerably below that, so that the numbers  
25 would be even less.

1 DR. HIRSCH: But these people were kept  
2 on it for a year or thereabouts. So we know --

3 DR. WHISNANT: Same dose without being  
4 allowed to change doses.

5 DR. HIRSCH: Right.

6 DR. CARA: Now, on comparator studies,  
7 you were allowed to titrate, is that not correct?

8 DR. WHISNANT: The titration period was  
9 up to month zero which was the period of  
10 maintenance. After they entered the 12 month  
11 maintenance period, there was no dose adjustment.

12 DR. FLEMING: Dr. Cara's question  
13 certainly leads us to this next discussion point.  
14 It's realizing, of course, that the response of  
15 individual patients is highly variable depending on  
16 their current level of glycemc control, their  
17 exposure to previous treatment. There may be a  
18 slight even gender difference between women and men.

19 At this point, we would like to explore  
20 what the state of your data would allow us to  
21 conclude about more refined dose regimen  
22 recommendations, and what studies might be needed to  
23 pursue other refinements.

24 DR. WHISNANT: Thank you very much, Dr.  
25 Fleming.

1           Let me go through this introduction very  
2 fast because I think so much of this has been  
3 discussed already in one way or the other, and then  
4 show you a tiny bit of some analysis, some of which  
5 you've seen already. So, this will be a fast  
6 response to the question, Dr. Fleming.

7           Obviously, the ideal in this setting is  
8 to give a drug which builds upon the natural intact  
9 feedback mechanism whereby insulin controls the  
10 glucose load and remains sensitive to the glucose  
11 load, and therefore would presumably not encounter  
12 the exogenous, idiopathic if you will, physician  
13 induced hypoglycemia because of these drugs.

14           Our hypothesis is that therefore, this  
15 insulin profile in red -- which looks very much like  
16 the dotted line insulin profile which is the natural  
17 meal related insulin profile induced by in this  
18 case, four milligrams of our drug -- should be a  
19 better approach to not only short-term FBG response,  
20 long-term glycemic control but hopefully, more  
21 physiologic in its patrol mechanism.

22           What we have therefore provided, what we  
23 believe we are providing with this drug is in  
24 effect, an individualized or patient controlled  
25 flexible dosing almost based upon the kind of

1 paradigm that's been developed for analgesics and  
2 potentially other drugs where patients learn to take  
3 care of themselves by taking a dose before each  
4 meal. They actually can take it anywhere up to 30  
5 minutes before beginning each meal without changing  
6 the PK profile or they will show you the blood sugar  
7 data, Dr. Cara. That dose should be managed  
8 according to the patient's eating schedule and that  
9 smaller doses give lower insulin responses and we  
10 know that from dose response studies.

11           So, theoretically as we go forward with  
12 this drug, we ought to be able to customize the  
13 amount of insulin response needed based upon how  
14 much the patient is taking in at that particular  
15 time. I hasten to tell you that study has not been  
16 done, but we look forward to doing it. And as Dr.  
17 Damsbo showed you that doses can be taken two,  
18 three, or four times a day without compromising  
19 either the glycemic control or the threat of  
20 hypoglycemia.

21           Then the final point on this slide is  
22 one that I'd like to comment on, again, with  
23 hopefully a little more clarity than I have this  
24 morning. The question of whether or not dose  
25 titration is required relates, we believe, to the

1 question of does the hypoglycemia of this drug  
2 profile suggest less severe, less frequent, or  
3 certainly less frequent, less severe hypoglycemias  
4 than with other therapies? If that is the case,  
5 then dose titration perhaps can be omitted, dosing  
6 can be simplified at least for certain patients  
7 where their risk of hypoglycemia is not as high.  
8 So, I return to the slides and a simplified version  
9 of those slides to formulate my request to you.

10           What I showed you this morning was that  
11 the percentage of patients having hypoglycemia is  
12 determined in part by their baseline HbA<sub>1c</sub> numbers  
13 relative to the dose group. These are previously  
14 treated patients where, at a four milligram dose  
15 with patients who have low HbA<sub>1c</sub>'s -- let's look at,  
16 say, the two lower dose groups between six and  
17 eight, all the way up to eight. What you can see is  
18 that the percentage of those patients reporting any  
19 hypoglycemic episode comes up -- approaches half the  
20 patients, as opposed to patients with higher HbA<sub>1c</sub>'s  
21 or patients who are -- for those previously treated  
22 patients. In contrast, the naive patients that we  
23 all know now are the more responsive patients have  
24 an even higher percentage of hypoglycemia,  
25 particularly those subsets who are eight and below,

1 and those patients who are given, if you will, full  
2 dose.

3 So that, our conclusions of this subset  
4 analysis of the data are that hypoglycemia risk is  
5 related both to the variable of previous treatment  
6 and to the variable of baseline HbA<sub>1c</sub>. So, if I put  
7 those variables on a slide for the four milligram  
8 dose group, what you can see is that the naive  
9 patients, these two bars, as well as the patients  
10 with a low HbA<sub>1c</sub>, have relatively higher  
11 hypoglycemia rates. In this case, probably an  
12 unacceptable rate of hypoglycemia compared to the  
13 previously treated patients and the previously  
14 treated patients who have higher contrast of that  
15 one milligram group, which I guess I don't have in  
16 there. It also shows this relationship, but with  
17 the bars proportionately lower.

18 What we're suggesting, therefore, is  
19 that it is this subset of patients, in fact, who  
20 need more therapy, if you will. Their response  
21 rates are going to be less and probably need more  
22 intensification of therapy. It's this subset of  
23 patients that perhaps we don't need to wait a month  
24 or six weeks to titrate because they're going to  
25 have a very acceptable rate of hypoglycemia even

1 with full four milligram dose.

2                   Now, it turns out that we tested the  
3 hypothesis in a European trial. This is a  
4 retrospective review of a piece of data. Because in  
5 a European trial, one of the comparator trials, the  
6 doctors who were carrying out this trial were  
7 allowed "at the discretion of the investigators,  
8 patients with greater than 160s while on previous SU  
9 were allowed to start on one milligram." The  
10 patients in one trial were allowed to start on  
11 titration at two milligrams three times-a-day with  
12 meals if they had blood plasma glucoses of greater  
13 than 180. So, we actually tested the percentage of  
14 hypoglycemia -- rather than test the titration  
15 design, these doctors actually tested the other  
16 answer without knowing it. So, they gave us a  
17 hypoglycemia rate for those patients that were  
18 started on .5, 1 and 2. It's 54 patients and it's  
19 four percent. So, it's not a big number, but what  
20 it says is that out of patients that were not in a  
21 purpose designed randomized trial but in patients  
22 who were, in fact, started on that dose, that the  
23 hypoglycemia rate is relatively low.

24                   So, our request for your consideration  
25 is that since we know these things about the rapid

1 insulin response with this drug, since we know that  
2 hypoglycemia events are not severe or serious, since  
3 we know the efficacy response is not only prompt but  
4 sustained, but is also dose related, we would ask  
5 for your consideration that in addition to a  
6 standard titration format of labeling that we  
7 consider whether or not it's rational to give those  
8 patients who meet certain clinical laboratory  
9 criteria the benefit of full dose of drug at the  
10 outset.

11 DR. HIRSCH: What is full dose at the  
12 outset?

13 DR. WHISNANT: Well, Dr. Kreisberg  
14 thinks it's two milligrams with each meal. In our  
15 clinical trials, the full dose was four milligrams  
16 with each meal. The delta between two milligrams  
17 and four milligrams is measurable on a dose response  
18 curve, but you know -- and is safe, clearly, four  
19 milligrams even four times a day and 20 milligrams  
20 four times a day did not have associated toxicities,  
21 either laboratory, EKG or symptomatic. And so, the  
22 four milligrams is well within the safety margin for  
23 dosing and it would be, you know, a doctor's  
24 decision about whether or not to give the full four  
25 milligrams.

1                   I guess what we would prefer is that the  
2 starting dose be two milligrams with each meal with  
3 the option of doubling that dose to determine if a  
4 patient has additional response.

5                   DR. HIRSCH: I was wondering what your  
6 best guess is, how much more than four milligrams?  
7 Because at four milligrams, you said half or not  
8 fully controlled, so it obviously has to be more  
9 than that.

10                  DR. WHISNANT: I just don't know because  
11 we've not done efficacy trials actually testing the  
12 difference between, say, four and eight four times-  
13 a-day. What we know is above four milligrams with  
14 each of four meals that the drug is safe, so we're  
15 not concerned about the margins. I believe our  
16 recommendation would be that for those patients that  
17 I've showed you on this subset analysis slide --  
18 that is, the previously treated patients with  
19 HbA<sub>1c</sub>'s below eight -- that two milligrams with each  
20 meal is an appropriate starting point and that the  
21 safety margin allows testing of at least twice that  
22 much for an individual patients based on response.

23                  DR. MARCUS: I'd like to ask a question  
24 that is directed to Dr. Fleming or Dr. Sobel. Many  
25 lacunae in our knowledge about this drug have come

1 up and without an answer except to say that this is  
2 a subject for future study. We're in an unusual  
3 position -- at least I feel in an unusual position,  
4 a little bit awkward about trying to make a  
5 recommendation to you as to whether this drug is  
6 ready to appear before the American public or not  
7 with all these lacunae in the background.

8 Now, I have not seen a guidance from the  
9 Agency about diabetes drugs. If one has been  
10 disseminated since my appearance, since my joining  
11 this panel, I'm not aware of it. Is it necessary  
12 and sufficient that a drug be shown to be  
13 indistinguishable in terms of the specific efficacy  
14 point that you've focused on, that is hemoglobin A<sub>1c</sub>  
15 and fasting plasma glucose, and that the safety be  
16 as the sorts of things we've heard about today? Or  
17 are we supposed to be considering that in all the  
18 rest of the material that many of us have expressed  
19 concerns about?

20 ACTING CHAIRMAN SHERWIN: This is the  
21 question I think all of us have.

22 DR. FLEMING: Well, by the way, we are  
23 working on a guidance for development of oral  
24 diabetic agents. I think the basic principle is in  
25 terms of demonstrating efficacy, that a clinically

1 significant change in glycemic control needs to be  
2 demonstrated. That is necessary and sufficient for  
3 demonstrating efficacy.

4 Then it comes to evaluating safety.  
5 Everything is germane to that, the theoretical and  
6 known risk. Though we may compare a therapy with  
7 currently available therapies, that does not  
8 necessarily mean that -- or we're not actually  
9 formally involved in that kind of comparison, but  
10 it's hard to avoid. You certainly are going to be  
11 comparing a new therapy with what is out there.

12 So, ultimately, it is the risk benefit  
13 that determines the approvability of the drug. You  
14 would start by showing a minimal level of glycemic  
15 improvement. Of course, glycosylated hemoglobin is the  
16 endpoint of choice for that. Certainly, the company  
17 has gone far beyond what would be considered a  
18 minimally acceptable change. Then it's a matter of  
19 making an estimate of the risk involved. At this  
20 point in the drug development, we certainly don't  
21 expect to answer all the questions. There will be  
22 significant questions that have to be answered as a  
23 larger population is exposed. But certainly, you  
24 need to have most of your safety issues at a  
25 reasonably defined state.

1 DR. MARCUS: Thank you.

2 ACTING CHAIRMAN SHERWIN: You showed us  
3 pictures of insulin going up and down and the  
4 implication is that the drug is causing those kinds  
5 of fluctuations to allow physiologic responses. Do  
6 you have any data with other sulfonylureas? I mean,  
7 you showed us the drug levels which I agree would be  
8 a higher with, let's say, glyburide as an example.  
9 Clearly, the drug levels are much higher and  
10 sustained for a longer period of time.

11 What's the impact on the profiles of  
12 those sustained higher levels? Because my  
13 impression is that you see the same sort of  
14 fluctuations in insulin with glyburide and glipizide  
15 and the other sulfonylureas, even though they have a  
16 longer duration of action. Is that sufficient to  
17 say that the drug is just working at that meal time?

18 DR. WHISNANT: Far be it from us to  
19 contradict your impression, sir.

20 ACTING CHAIRMAN SHERWIN: No, no, no,  
21 no, I -- something out of it.

22 DR. WHISNANT: Our understanding is that  
23 the normal meal related fluctuations in insulin,  
24 which we have demonstrated over and over again  
25 because we have placebo comparisons for each of

1 those curves. So, the normal meal related  
2 fluctuation is still intact when you give this drug,  
3 or when you give any drug.

4 ACTING CHAIRMAN SHERWIN: Right.

5 DR. WHISNANT: The question really is,  
6 is there a difference at nadir and is there a  
7 difference at night?

8 ACTING CHAIRMAN SHERWIN: Right.

9 DR. WHISNANT: Because that's the time  
10 when the long acting drugs cause trouble.

11 ACTING CHAIRMAN SHERWIN: Right. And my  
12 question is that I didn't see that data, or did I  
13 see it between --

14 DR. WHISNANT: We haven't studied other  
15 people's drugs.

16 ACTING CHAIRMAN SHERWIN: You've not  
17 compared the other drugs?

18 DR. WHISNANT: Well, Dr. Damsbo showed  
19 you a small study looking at the skip-a-meal  
20 hypothesis.

21 ACTING CHAIRMAN SHERWIN: Right, but  
22 that has some problems with it. But in terms of  
23 other kinds of studies, looking at 24 hour profiles,  
24 we don't have that data. Is that right?

25 DR. WHISNANT: We do not have that data

1 in our database.

2 ACTING CHAIRMAN SHERWIN: Right.

3 DR. WHISNANT: We did not --

4 ACTING CHAIRMAN SHERWIN: Not that I'm  
5 saying -- you may not have been asked to provide  
6 that data.

7 DR. WHISNANT: That's okay.

8 ACTING CHAIRMAN SHERWIN: You know, so  
9 I'm not trying to say that, you know, this is your  
10 fault for not showing that data. I'm just curious  
11 about it because the implication is that the insulin  
12 levels will be higher with some of the other  
13 sulfonylureas at night. I think theoretically,  
14 that's so. The issue is, you know, it would be nice  
15 to know that in a more defined way.

16 DR. WHISNANT: The theoretical concerns  
17 based upon the kinetic profiles of the drugs I  
18 suspect people can dig out that information from  
19 various studies that have been done previously. But  
20 let me clarify that we did not come to the Agency to  
21 make a superiority claim. We came to the Agency for  
22 efficacy and safety of this drug. If we were going  
23 to go to the next level, if you will -- sorry, Dr.  
24 Marcus, but this would be a future question that we  
25 would have to address in order to make a superiority

1 claim.

2 ACTING CHAIRMAN SHERWIN: Sure. Right.

3 And the Agency is not looking for superiority  
4 decision in terms of efficacy.

5 DR. FLEMING: Oh, absolutely not.

6 That's a very important point. The company is only  
7 obliged to show safety and efficacy. If they want  
8 to make a superiority claim, they would have to have  
9 the data that demonstrate that the drug is actually  
10 superior to a given therapy. Now, it wouldn't have  
11 to be necessarily confined to efficacy. They could  
12 formally demonstrate that hypoglycemia, for example,  
13 was reduced with comparable efficacy achieved. That  
14 would be another means of getting a superiority  
15 claim in effect. But the company is not making that  
16 case here.

17 ACTING CHAIRMAN SHERWIN: Right.

18 DR. WHISNANT: I would add though that  
19 we believe we have the basis, theoretically,  
20 scientifically, with clinical signal to do that.  
21 So, I mean, while that purpose design study is not a  
22 part of this application, we believe that it is now  
23 rational to do that.

24 ACTING CHAIRMAN SHERWIN: Right. I  
25 guess it relates to claims when drugs are released

1 and advertising is --

2 Dr. Nisben, welcome.

3 DR. NISBEN: I'd just like briefly to  
4 respond to what Dr. Marcus had asked. I am actually  
5 working on a guidance for development of diabetes  
6 drugs. Also, I think with respect to this  
7 particular product, we are supposed to have two  
8 adequate and well controlled trials demonstrating  
9 efficacy. But I think it should be pointed out that  
10 that's adequate and well controlled trials  
11 demonstrating efficacy in the population which is  
12 intended to be treated. I think that's something  
13 which has not been adequately discussed in my  
14 opinion.

15 Most of the studies that have been  
16 presented have been in patients who have been poorly  
17 responsive to sulfonylureas, the comparative trials  
18 -- and I think as Dr. Cara has said very, very well,  
19 they were poorly controlled when they began. They  
20 were even worse controlled at the end. So, really,  
21 one can't say anything about efficacy in those  
22 trials.

23 When you look at the other trials to  
24 placebo control trials, although it appears that  
25 there are three adequate, well controlled trials, I

1 really don't think that's the case. The number of  
2 naive patients is extremely small. The total  
3 exposure is only about 100 patients. We've already,  
4 I think, come to the conclusion that this is not a  
5 drug that you're going to take patients off of  
6 glyburide and put them on repaglinide because we  
7 know that they don't do any better.

8           This is really the intent, it seems to  
9 me, is to use this drug in naive patients. But  
10 where's the data? Where's the database to show that  
11 it's effective in naive patients? Well, it probably  
12 is, but the number of patients exposed is very  
13 small. Also, I think the intent is to decrease  
14 hypoglycemia and I think as Dr. New pointed out, it  
15 would be very, very, very, very nice to be able to  
16 take a drug before each meal. And if you skip a  
17 meal, you wouldn't take it and you would  
18 theoretically prevent hypoglycemia. But from the  
19 data we showed, it looked to me like if anything,  
20 the risk of hypoglycemia might actually be worse in  
21 the naive patients. Those were the ones that had  
22 the most robust responses.

23           It seems to me we do not have long-term  
24 data on those patients. The total database is only  
25 about 100. It seems to me that it is a perhaps a

1 bit premature to be releasing this on the American  
2 public. I don't know of any other oral hypoglycemic  
3 agent where the total database for the intended  
4 population is really so very, very small. This, I  
5 think, would be a first.

6 DR. FLEMING: I think it's good that we  
7 can have different opinions within the Agency.  
8 Obviously, Dr. Nisben has stated his opinion.

9 I actually take a different slant from  
10 what you just heard. I think the intended  
11 population is what was tested. Basically, this  
12 treatment will be offered to more patients that have  
13 been on other agents than not. This is just a  
14 reality. So, there was nothing wrong in the  
15 population that was selected. That's simply a  
16 reflection of the current situation today.

17 Now, you could say that we don't have  
18 enough naive patients period, in an absolute sense,  
19 to say what the degree of efficacy will be. I don't  
20 think anyone would believe that naive patients would  
21 respond any less than patients who have been treated  
22 with other agents before. So, I'm not sure that we  
23 have a concern that the drug would be less  
24 efficacious in naive patients. I'm not sure what  
25 the value of a huge study that simply was confined

1 to naive patients would be. We would probably find  
2 that these patients responded somewhat better on  
3 average than this mixed population that has been  
4 studied.

5 But in terms of my opinion about the  
6 company's placebo controlled studies, I do think  
7 that they would represent studies that are adequate  
8 to support efficacy.

9 DR. CARA: You were going to show us  
10 some blood glucose data to support the statement  
11 regarding timing of the dosing.

12 DR. NEW: They showed it when you were  
13 out of the room.

14 DR. CARA: Oh. Could somebody fill me  
15 in on what it showed?

16 DR. NEW: No difference.

17 DR. CARA: No difference.

18 ACTING CHAIRMAN SHERWIN: Cathy and then  
19 Maria.

20 DR. CRITCHLOW: If I could just get a  
21 clarification on the placebo controlled trials?

22 Since the percentage of naive patients  
23 was very small, were these then patients who were  
24 being treated with something and then taken off of  
25 that treatment? And they were the controls?

1 DR. WHISNANT: Naive in our definition  
2 of inclusion criteria for the clinical trials means  
3 that they have by ADA criteria type 2 diabetes  
4 mellitus, but have not been previously treated with  
5 an oral hypoglycemic agent.

6 DR. CRITCHLOW: Right. And that  
7 percentage was small in the --

8 DR. WHISNANT: Well, it's in the --

9 DR. CRITCHLOW: I mean, was it 23  
10 percent?

11 DR. WHISNANT: -- comparator trials,  
12 it's on the order of 12 to 15 percent of --

13 DR. CRITCHLOW: But in the placebo  
14 controlled --

15 DR. WHISNANT: -- 2,000 patients, and in  
16 the placebo controlled trials it's --

17 DR. CRITCHLOW: Well, it's nine or 23.

18 DR. WHISNANT: What's the percentage in  
19 65 and --

20 257 naive patients treated with  
21 repaglinide in various trials.

22 ACTING CHAIRMAN SHERWIN: Okay. Maria  
23 and then we'll go on to the fourth question.

24 DR. WHISNANT: Can I just offer one more  
25 comment about that question, please, Dr. Sherwin?

1                   I'd just like to offer in response that  
2                   the number of patients required, to some extent,  
3                   depends on the delta because after all, it's  
4                   statistical difference that we're asked to  
5                   demonstrate a clinically meaningful and  
6                   statistically significant difference. So, because  
7                   response in naive patients is quantitatively so much  
8                   different, then I could logically conclude that  
9                   perhaps not as many patients required in order to  
10                  satisfactorily demonstrate that therapeutic effect.

11                  DR. CRITCHLOW: No, I agree. But in the  
12                  non-naive patients and if they were in the placebo  
13                  arm, were they currently on therapy when they were  
14                  recruited for the trial and then taken off of  
15                  therapy for the duration of the trial? So, we  
16                  basically saw no difference in control with the  
17                  treated patients and, like you said before, an  
18                  obvious worsening of control in the placebo patients  
19                  among basically a large group -- the subset of  
20                  patients that were previously being treated who were  
21                  in the control arm who were essentially not being  
22                  treated for the purposes of the trial. So, the  
23                  difference that we're seeing is essentially taking  
24                  people who were being controlled to some extent, and  
25                  then being taken off --

1 DR. WHISNANT: Take them off therapy,  
2 and their disease gets worse. You compare them to  
3 continuing to maintain that on another therapy.  
4 That is correct.

5 DR. FLEMING: And I think that's an  
6 important point. These are not burned out patients.  
7 They, because of the protocol, had to demonstrate  
8 that they were receiving some benefit from the  
9 previous therapy.

10 ACTING CHAIRMAN SHERWIN: Maria, this is  
11 the last question.

12 DR. NEW: Cathy, are you saying that you  
13 would like to see a comparison of placebo versus  
14 treated in cohorts that have never been treated?

15 DR. CRITCHLOW: I think we saw --

16 DR. NEW: You never saw that because I  
17 think most of the placebo patients are withdraw  
18 patients. They are not never treated patients. In  
19 contrast to those that are treated with repaglinide,  
20 those patients who are considered naive are never  
21 treated patients.

22 Am I correct in my conclusion that your  
23 placebo group does not mean never treated? Only  
24 your treated group needs never treated in the naive  
25 group.

1                   ACTING CHAIRMAN SHERWIN: No. You've  
2 got me confused now.

3                   DR. WHISNANT: We're using words in a  
4 slightly different way, Dr. New.

5                   DR. NEW: Okay. Let me just ask my  
6 question and then I'll be clear, and I think that  
7 that will clear Cathy. Because then I want to ask  
8 my own question.

9                   When you call a study naive, I  
10 understand that those that you treat have never been  
11 treated before.

12                  DR. WHISNANT: That is correct.

13                  DR. NEW: Now, what about the placebo  
14 group?

15                  DR. WHISNANT: They've never been  
16 treated before either because it's a randomized,  
17 controlled, double-blind trial.

18                  DR. NEW: Okay, then I'm wrong.

19                  DR. WHISNANT: You take the population,  
20 whatever the population is --

21                  DR. NEW: I got it.

22                  DR. WHISNANT: -- it could be previously  
23 treated or naive, and you randomize them blind.

24                  DR. NEW: Okay. Here's my question, my  
25 question. It seems to me that your persuasive

1 powers to say that this drug is a good drug to give  
2 to the American public resides in three slides that  
3 you've shown. The first two slides of those that  
4 are your annual trials, patients treated for one  
5 year, those that are naive and those that are  
6 already treated. You showed two slides. The third  
7 is a table in which you demonstrated the  
8 hypoglycemic complication of the drug in that slide  
9 that has a table with 343 patients treated with  
10 Prandin and 131 treated with glyburide.

11 ACTING CHAIRMAN SHERWIN: That's the  
12 elderly, yes.

13 DR. NEW: Of the Prandin one, 65 percent  
14 reported symptoms and of that 65 percent that  
15 reported symptoms, eight percent actually measured  
16 their blood sugars. Am I right?

17 ACTING CHAIRMAN SHERWIN: No, no.

18 DR. WHISNANT: Eighty percent had very  
19 low --

20 ACTING CHAIRMAN SHERWIN: Documented  
21 glucohypoglycemia.

22 DR. NEW: That's right, had documented  
23 -- measured -- that's what I said, actually measured  
24 the blood sugars that were less than 45.

25 ACTING CHAIRMAN SHERWIN: Right.

1 DR. NEW: Okay. So, those numbers when  
2 you calculate them --

3 ACTING CHAIRMAN SHERWIN: Three  
4 patients.

5 DR. NEW: No, I don't get that. Out of  
6 343, 45 percent reported hypoglycemic symptoms.  
7 That comes to 154 patients. Of that, if you take  
8 eight percent of those that reported symptoms and  
9 then measured their blood sugars or documented their  
10 hypoglycemia biochemically, that's 12 patients.

11 ACTING CHAIRMAN SHERWIN: Somehow, we'd  
12 have to go back to the table. I'm not sure now.

13 DR. NEW: Okay, anyway, but can you pull  
14 those three slides and then I'll feel like I can  
15 make a decision?

16 ACTING CHAIRMAN SHERWIN: Okay.

17 While you're pulling those slides --

18 DR. NEW: That's the two annual slides  
19 and the table on hypoglycemia.

20 ACTING CHAIRMAN SHERWIN: Dr. Fleming,  
21 can we move on to the fourth because we're going to  
22 be here until tomorrow.

23 DR. FLEMING: Okay. Issue number  
24 four --

25 ACTING CHAIRMAN SHERWIN: We'll come

1 back to Maria's question at the end. I promise.

2 DR. FLEMING: Well, as the company has  
3 already pointed out, there was the observation of an  
4 imbalance in the number of myocardial ischemic  
5 events that were observed in not just one trial, but  
6 probably two.

7 Let's have the next slide. Perhaps it's  
8 the one before that or the one after. Let's go back  
9 -- yes, that's fine.

10 Now, this is the result from the US  
11 study with glyburide as the comparator. You can see  
12 that particularly when you get down to acute  
13 ischemic events as a subcategory of cardiovascular,  
14 that there is a fairly high relative risk. This is  
15 the risk compared to the comparator group,  
16 glyburide. On the other hand, the statistical  
17 significance is trending, but it is certainly not  
18 reaching the point that we would conclude that it  
19 has reached statistical significance.

20 Now, in the next slide this simply sums  
21 up the unadjusted and adjusted relative risk with  
22 respect to these various comparators, including  
23 placebo. You can see that with respect to glyburide  
24 in particular, there is an adjusted relative risk of  
25 about two times. Even in the case of placebo, there

1 is an adjusted relative risk that approaches two.  
2 So, this is our signal. This is unexpected in the  
3 sense that we did not expect to see a difference  
4 between these treatment groups. They work in  
5 basically the same general way. Obviously, everyone  
6 knows about the story of UGDP and the cloud that  
7 that study has cast on sulfonylurea therapy as well  
8 by guanides by the way. Phenformin was involved in  
9 that trial, I'll remind you.

10 At any rate, these are what we have. We  
11 do not have, certainly, statistical significance.  
12 When you meta-analyze the entire trials, basically,  
13 these effects wash out.

14 Now, the question is what do we do at  
15 this point. I think it would be now time for the  
16 company to respond with how they would view these  
17 data, and more importantly, what you would do to  
18 resolve the issue.

19 DR. WHISNANT: Thank you very much, Dr.  
20 Fleming. We're happy to respond to this.

21 It's a serious signal that we've  
22 listened to, watched for very carefully. Let me  
23 remind you first that Dr. Edwards spoke to the  
24 cardiovascular risk profile for this drug when he  
25 concluded that our risk profile for cardiovascular

1 events is similar to comparable to sulfonylureas.  
2 But that we have a small increase of non-fatal  
3 events, a count phenomenon. The number is  
4 increased, non-fatal events in comparison to  
5 glyburide.

6 So, having seen that signal, we went  
7 through the detailed analysis that Dr. Edwards  
8 showed you a couple of slides on. I'd just like to  
9 remind you that this is the cumulative incidence  
10 curve that he showed you for all trials, for all  
11 ischemic events, normalized to the 049 study in the  
12 United States. The reason why that's important is  
13 that the 049 study actually has in it another  
14 unequal randomization -- not an imbalance in the  
15 randomization that was simply a fact of the kinds of  
16 patients who are recruited into this trial. I  
17 remind you that this was a randomized, controlled,  
18 double-blind trial so there was no control as to  
19 stratification over these kinds of baseline events.

20 There were 12 patients in the  
21 repaglinide group who had had prior MIs, six  
22 patients who had had congestive heart failure, five  
23 patients had at baseline ischemic changes on their  
24 EKGs, and 17 patients with a medical history of  
25 coronary artery disease. As opposed to in half as

1 many patients now in the glyburide group, two with  
2 prior MIs, one with EKG ischemia and four with  
3 coronary artery disease.

4 I do not show you this slide in order to  
5 deny the signal of cardiovascular disease that we  
6 have seen in our trials. Whatever the imbalance was  
7 in the trial, we have taken the signal and taken it  
8 very seriously.

9 DR. MARCUS: Is that, by the way, a post  
10 hoc analysis?

11 DR. WHISNANT: That's a post hoc  
12 analysis. All the histories were reviewed  
13 independently, I might add. All the EKGs were  
14 reread independently and this analysis was  
15 constructed because we saw the signal. All the data  
16 had been collected prospectively, but then we went  
17 back and reviewed the case report forms in order to  
18 look at these kinds of numbers.

19 Now, I also remind you that developing  
20 drugs in this arena means that we're working in this  
21 kind of environment. We recognize the environment  
22 in which we work where if we treat enough patients -  
23 - if we treat 100 patients for a year, 5.5 percent  
24 of them on average are going to die. This is  
25 cumulative mortality figures from the ADA, from the

1 national follow-up study that's reported in the ADA  
2 manual. I also remind you that depending on how  
3 many patients we have in the old rates group, then  
4 our mortality will be higher.

5 The range of cardiovascular events that  
6 we're dealing with in these kinds of trials is  
7 represented on this sort of survey, list,  
8 compilation. It runs from 1.6 percent total  
9 mortality in the 50 age decade up to as high as six  
10 percent in another prospective microalbuminemia  
11 study.

12 Now the company has taken this  
13 challenge, this signal, this worry, if you will,  
14 very seriously. We've met with the Agency to  
15 discuss the analysis of the data and we come here  
16 today to show you a proposal that we believe  
17 adequately addresses the ongoing need for assuring  
18 the safety profile of this drug. I know of no  
19 better person to address this issue than Dr. Gerry  
20 Faich.

21 Sir?

22 DR. FAICH: Mr. Chairman, ladies and  
23 gentlemen, what I would like to do is describe for  
24 you how this expert committee that you see listed  
25 here which I chaired approached this issue of

1 cardiovascular risk in type 2 diabetes, and  
2 approached the issue of designing a study, at least  
3 in outline form. I'm going to be very brief because  
4 we deliberated through a number of things and I'd  
5 like to at least share that process with you as  
6 opposed to sharing with you a completely finalized  
7 study.

8 I need to point out at the outset that  
9 our group, having seen these same data, was  
10 reasonably ambivalent about whether this was a  
11 meaningful signal to begin with. So, what I'm going  
12 to do is assume that there is a possible problem and  
13 that what one is involved with here is, in a sense,  
14 proving a negative.

15 We also knew at the outset that when one  
16 talks about oral hypoglycemic agents and type 2  
17 diabetes, the UGDP remains with us as you all know.  
18 I might just remind you that was a study with 200  
19 patients per arm, total of five arms depending in  
20 part how you counted. The study went on for six or  
21 eight years, again, depending at which point you  
22 thought the study was actually terminated. So, in  
23 that instance, we're talking about 8,000 person  
24 years to get to the conclusions that were raised,  
25 and you well know those conclusions suggesting that

1 tolbutamide had twice the cardiovascular mortality.  
2 That now appears as class labeling in oral  
3 hypoglycemics.

4           The other thing that we recognized as a  
5 background issue is that in the face of UGDP and  
6 around some of the other issues that you all have  
7 been discussing, one of the really epidemiologic and  
8 medical and therapeutic issues is what is the  
9 natural history of treated type 2 diabetes. We all  
10 know that that's the critical issue. We didn't  
11 think for a moment that we were going to be able to  
12 get answers to all those questions in the design of  
13 this study. We targeted the study to ask the  
14 question of what is the cardiovascular risk of  
15 repaglinide and appropriate comparitors? Let me  
16 show you how that process went.

17           I might just say, the expert committee  
18 was made up of Sean Dinneen from the Mayo Clinic who  
19 brought some epidemiologic background around the  
20 expected background rates because that was an issue  
21 powering the study. Saul Genuth has previously  
22 served on this Advisory Committee and was on the  
23 board for the DCCT. Bob Makuch is chairman of  
24 biostatistics at Yale, and Jamie Rosenzweig has  
25 participated in many clinical trials of diabetes at

1 the Joslin Clinic.

2           Before we started, we did ask ourselves  
3 what other Phase IV approaches are available to  
4 looking at the performance of a compound in the  
5 marketplace. Of course, the usual epidemiologic  
6 observational methods including passive  
7 surveillance, prescription event monitoring, and  
8 other registry and cohort approaches and case  
9 control studies are out there. Just to cut to the  
10 quick on that, the issues in all of them is  
11 selection bias. Without a randomized control  
12 process, we felt that it would be hopeless to use  
13 epidemiologic methods around the issue of  
14 cardiovascular associated events in type 2 diabetes  
15 long-term.

16           That took us quickly to talking about  
17 and discussing a randomized, but simplified,  
18 clinical trial. We recognized, as I've already  
19 said, that this was destined to be a very large  
20 undertaking. It would demand, by definition,  
21 internal comparator comparitors. That there were  
22 some very real feasibility issues but, in fact, at  
23 the end of the day if one wants to ask these kinds  
24 of questions, that's probably the only real option.

25           Bruce Stadel here at FDA as well as

1 Patrick Waller and others in thinking about and  
2 talking about Phase IV studies, when they were  
3 discussed, pointed out -- and I like these points  
4 very much. I think they're most appropriate -- that  
5 one wants to be mindful that the study be conducted  
6 in representative populations, that you choose the  
7 right endpoints that are meaningful. More often  
8 than not, that means hard endpoints that are less  
9 subject to observer bias and other sorts of biases.  
10 That the studies be sufficiently powered and yes,  
11 that the results come in in your lifetime and mine  
12 and that they not be historical undertakings. So  
13 that timeliness of the study as well as duration,  
14 appropriate duration, so that one can look at long-  
15 term effects are important points to consider in the  
16 design of such studies.

17           The one point that's not on here is that  
18 one also ought to choose appropriate -- and that  
19 means clinically, real world practice appropriate  
20 comparitors. So, our group met and we began  
21 discussing what comparitors do we feel are  
22 appropriate and essential. We discussed at length  
23 in terms of entry criteria, would one want to  
24 restrict this to if not naive type 2 diabetics,  
25 naive to oral hypoglycemics, then indeed, patients

1 who did not have a history of cardiovascular  
2 disease. We, in fact, concluded that in the spirit  
3 of being representative as well as the  
4 simplification process, that one ought to take, in  
5 effect, all comers and not use a restrictive  
6 approach to entry criteria.

7           We felt that the endpoints of critical  
8 interest were cardiac hospitalizations and all-cause  
9 mortality. We discussed at some length what  
10 stopping rules might look like and some of the  
11 ethical issues, not unlike some of the discussions  
12 about placebo. We feel -- and just to mention it  
13 here -- that conducting this with a no treatment  
14 placebo arm would be, at this point of the state-of-  
15 the-art and science of treating type 2 diabetes,  
16 would be unethical. I'm glad to see a couple of you  
17 nodding because theoretically, that would be ideal  
18 and we don't question that. But we think it's not  
19 appropriate and not on.

20           We recognized that one would have to  
21 target the several arms toward achieving reasonably  
22 comparable therapeutic goals in terms of blood  
23 glucose and hemoglobin A<sub>1c</sub>. There are issues there  
24 about how tightly you run the trial and how tightly  
25 you measure those endpoints. We would view that as

1 a variable to enter into the analysis as opposed to  
2 one that one wants to target to a fixed level. We  
3 discussed secondary endpoints particularly including  
4 therapeutic failure rates and serious hypoglycemia,  
5 not least around some of the issues that you all  
6 have been discussing here and recognize what we're  
7 talking about here would be, if you will, a  
8 population, a very large population, followed over  
9 time in actual practice, as it were.

10 So, that was all by way of background.  
11 The next issue that we grappled with at length, and  
12 I've been talking around it here in these few  
13 moments, was how large does such a study have to be?  
14 The size is going to be driven by the number of arms  
15 of the study, the level of statistical power. We  
16 basically said this ought to have 80 percent power  
17 with a p of .05. The relative risk issue here is  
18 that this is, in effect if we're talking  
19 cardiovascular endpoints in equivalence trial --  
20 that is, we would be targeting to demonstrate a  
21 relative risk of one with, yes, a confidence limit  
22 around it that we selected as .07 to 1.3. As one  
23 narrows that confidence limit, by the way, the size  
24 of the study goes up logarithmically.

25 We discussed what would be a practical,

1 reasonable, appropriate and useful length of follow-  
2 up and we chose a period of three years of patient  
3 observation, recognizing there would probably be a  
4 one-year period of enrollment. So, on average, you  
5 would have 42 months or three-and-a-half years of  
6 time, person time, per each individual in the study.  
7 I might just say that one of the reason we came to  
8 that is we felt that after three or four years of  
9 following patients, patient crossover to other  
10 drugs, patient migration, issues of loss to follow-  
11 up and the like would become very real. Also, in  
12 the spirit of timeliness, we would rather have more  
13 patients for a relatively shorter period of time  
14 than a smaller number of patients for a much longer  
15 period of time. Obviously, a set of compromises. I  
16 don't think there are any hard and fast rules in  
17 that.

18                   We also talked about what would be in  
19 the one of the determinants, maybe one of the main  
20 determinants of sample size is what's the expected  
21 background rate of cardiac hospitalizations in all-  
22 cause death? We took as four percent to power the  
23 study. We did examine a range actually down from  
24 three to up to five percent of rates. You saw in  
25 the slide that John Whisnant presented a moment ago

1 where we looked at the data sources to get those  
2 estimates. It included the UK prospective diabetes  
3 trial, the WISTAR, Wisconsin epidemiologic  
4 ophthalmic study, et cetera.

5           Lastly, we discussed at some length  
6 practical limitations of conducting the study in  
7 terms of everything ranging from patient eligibility  
8 to what kinds of materials would be provided to  
9 patients? How would drug be provided? Where would  
10 the sites come from and the like? I don't intend to  
11 go into all of those details here. Having said all  
12 of that, this is the study that we propose at this  
13 point. We have discussed this with FDA and let me  
14 just walk you through this because this ought to be,  
15 perhaps, a one slide presentation and this is it.

16           The study we would propose would enroll  
17 type 2 naive or previously treated type 2 diabetic  
18 patients previously treated with oral hypoglycemics  
19 who have a hemoglobin A<sub>1c</sub> equal to or greater than  
20 eight. The only age restriction we would put on it  
21 would be greater than or equal to 45, simply because  
22 the events of interest are going to be much less  
23 frequent below that age group. Ideally, we would  
24 like to have this population be representative of  
25 the type 2 diabetic population in the US.

1                   We proposed a three arm study which  
2                   would be achieved through randomization,  
3                   repaglinide and equal size of arms, insulin and  
4                   glipizide. The study would be, as I've said, three  
5                   years in duration in terms of patient observation.  
6                   That is, each patient but since there would be a  
7                   patient enrollment here, that would translate into  
8                   three-and-a-half years on average of patient  
9                   observation. So, that would give us something on  
10                  the order of 20,000 patient years of exposure.  
11                  Again, this is an enormously large undertaking,  
12                  needless to say.

13                  In part, as a consequence of that, the  
14                  data variables collected at baseline -- we would  
15                  collect all of the appropriate and important  
16                  covariates. But then along the way, we would  
17                  restrict data collection to those endpoints of  
18                  critical interest. We would get baseline hemoglobin  
19                  A<sub>1c</sub>'s and do that annually. EKG at baseline, again  
20                  for allowing for analysis by that covariate. We  
21                  would collect the endpoints of interest meaning  
22                  cardiac hospitalizations, any changes in drug  
23                  therapy, any episodes of hypoglycemia and death. We  
24                  propose that the Drug Safety Board would meet at the  
25                  end of the first year and then at six month

1 intervals, and would be armed with the usual kinds  
2 of interim analyses and stop rules.

3 So, that's a very quick overview of  
4 what's proposed for study. We feel this study would  
5 indeed meet the requirements of representative  
6 population, timeliness. We feel it is feasible as  
7 described and it has the appropriate comparitors.  
8 Needless to say, we discussed these comparator arms  
9 at length in terms of what the several options might  
10 be and we're prepared to discuss that if that seems  
11 appropriate here.

12 Well, just to summarize what I've  
13 described here in very outline fashion is a proposal  
14 for a randomized, simplified clinical trial. It  
15 would be obviously multicentric and perhaps  
16 multinational. Exposure would be, on average,  
17 three-and-a-half years. The comparitors are, as  
18 mentioned, repaglinide, insulin, glipizide. Primary  
19 endpoints cardiac death, hospitalization for acute  
20 cardiac disease, all-cause mortality. Secondary  
21 endpoints would be hypoglycemia and treatment  
22 failures.

23 Let me, before I take questions, invite  
24 Dr. Kurt Furberg who is known to many of you and is  
25 a most prominent clinical trialist and cardiac

1 epidemiologist to make some comments. Then both of  
2 us would entertain your questions.

3 DR. FURBERG: Thank you, Gerry.

4 Mr. Chairman, colleagues, I was asked by  
5 the sponsor to take a look at the cardiovascular  
6 event data. I think the charge to me was to give  
7 some advice as to whether the observed findings  
8 represented noise of random variation or a true  
9 signal. The limitations of that are quite obvious:  
10 small numbers, different trials.

11 My first approach was to look at the  
12 totality of the evidence, to look at the three  
13 outcomes, all cardiovascular events, the serious  
14 cardiovascular events -- which is a subset of the  
15 all cardiovascular events -- and then trimming it  
16 down even more to the acute ischemic events. You  
17 already heard that there were differences between  
18 the trials and within the trials, so I think the  
19 proper way of looking at that is to consider the  
20 adjusted analyses.

21 If I look at the all cardiovascular  
22 events, look at the repaglinide versus all  
23 comparitors pooled in adjusted analyses and I focus  
24 on all cardiovascular events, I get a risk ratio of  
25 1.14 which is very, very close to unity. But in

1 doing so, I realize that all cardiovascular events  
2 is a mixed bag, including symptoms like  
3 palpitations, findings from physical exam like  
4 murmur, and then serious events. So, it makes sense  
5 to try to focus the analyses on the more important  
6 events.

7 So, if we move down then to the serious  
8 cardiovascular events, again, pooled analyses, the  
9 risk ratio goes up. It's 1.55, but the confidence  
10 interval includes unity. So, the difference is not  
11 statistically significant. Still in that group, I  
12 defined events like peripheral ischemia, thrombotic  
13 events, cerebrovascular events, arrhythmias, atrial  
14 fibrillation. Again, a fairly mixed bag. It's  
15 hard to think about a mechanism by which the drug  
16 could cause these problems.

17 So, looking at the acute ischemic  
18 events, again, pooled analyses, risk ratios, almost  
19 at unity, 1.02. That composite outcome includes  
20 angina -- particularly angina leading to  
21 hospitalization, acute myocardial infarction,  
22 coronary artery disease, and myocardial ischemia.  
23 So, in commenting on the totality of the evidence, I  
24 would say I don't see any significant overall  
25 increase in adverse cardiovascular events in the

1 completed trials.

2 I agree with the approach taken that you  
3 also need to look at the individual comparitors  
4 including placebo. You may want to look at the  
5 individual trials, but limitations methodologically  
6 are even more apparent. The numbers that were small  
7 to start with are getting smaller, and the findings  
8 are more susceptible to imbalances that we've heard  
9 about. They increased what here is the multiple  
10 comparisons. I don't know how many we have, but  
11 probably 30 or 40. To assign appropriate level of  
12 significance is apparent. When I look at the  
13 findings, I don't see anything that is consistent.  
14 So, my conclusion is that the findings of the  
15 individual trials should be interpreted cautiously.

16 In conclusion, I do not believe that the  
17 available cardiovascular event data should be a  
18 reason for concern. I've always been, for now 25  
19 years, a proponent of large long-term trials and I  
20 really welcome the commitment by the sponsor to  
21 support the big trial. I think it's important from  
22 a clinical point of view, public health point of  
23 view, to get data on cardiovascular mortality and  
24 morbidity from a comparison of repaglinide and the  
25 other standard treatments available today. Ideally,

1       like you, I would have liked to see a placebo  
2       control trial but that is not feasible. That was  
3       underscored at a meeting that I attended about a  
4       month or so ago, a special emphasis panel sponsored  
5       by the National Heart, Lung and Blood Institute.

6                So, I think the trial is recommended. I  
7       think it's the best we can do. It's a major  
8       commitment, major advance, as I see it. If we see a  
9       difference favoring one treatment or another, that  
10      could have major implications for the treatment of  
11      type 2 diabetes. I think what the company can do is  
12      pray that they come out ahead. They should be  
13      satisfied if they are equal and take the  
14      consequences if they come out as losers. Thank you.

15               ACTING CHAIRMAN SHERWIN: Dr. Kreisberg  
16      and then Dr. Marcus.

17               DR. MARCUS: I need to go to the  
18      airport, so can I play through?

19               DR. KREISBERG: Yes.

20               DR. MARCUS: I liked that study very  
21      much, but I'm worried about one issue related to  
22      recruitment and retention. That is, it seems a  
23      little bit inflexible for patients who might be  
24      uncontrolled on any of these drugs you're assigning  
25      them except insulin where, of course, a dose could

1 be very flexible.

2 I wish there were some way you could  
3 build into it that a person who is assigned to one  
4 of the oral agents could have added to their  
5 regimen, metformin or troglidazone, some sensitizer.  
6 I assume you've considered it. Is there any way to  
7 work it in?

8 DR. FAICH: The answer is we discussed  
9 that and I don't think we've come to final  
10 conclusions on it. But there's little doubt that  
11 one will have to have some kind of rescue therapy --  
12 that's not quite the right word, but augmentation  
13 therapy for many of these patients and we recognize  
14 that. That makes the analysis difficult, but on the  
15 other hand, if you look at this as an intent-to-  
16 treat from the start across the three arms, that's  
17 what we would propose to do.

18 The other thorny issue in this is how do  
19 you control for level of hemoglobin A<sub>1c</sub> achieved as  
20 the critical confounder without, in fact, driving  
21 the treatment? The place we came to on that is, we  
22 said set treatment goals, encourage the achievement  
23 of those goals, and then deal with it in the  
24 analysis. But it's an extraordinarily difficult --  
25 both those questions were difficult for us.

1 DR. KREISBERG: It's an interesting  
2 undertaking because the baseline risk of the  
3 patients is high. Rather than introducing a therapy  
4 that is expected to lower the risk, you're actually  
5 introducing a therapy that may increase the risk  
6 further. So, it's different from a lot of previous  
7 trials.

8 But the thing that strikes me is, how do  
9 you randomize these patients? Because if they're  
10 randomized simply as first come, first served into  
11 the various treatment arms, how do you guarantee  
12 that the coronary heart disease risk factors, which  
13 probably are more important than the diabetes or  
14 even the therapy in determining a risk, are equal  
15 among the groups?

16 DR. FAICH: The ideal way to do that, of  
17 course, would be do a block stratified randomization  
18 on the front end to be sure that if someone has risk  
19 factor, they have equal opportunity. We talked  
20 about that and I don't think we've completely ruled  
21 it out. We felt that this was an issue, given 2,000  
22 patients per arm, it was highly unlikely in contrast  
23 perhaps to the much smaller trials we've been  
24 hearing about today that we would get a  
25 maldistribution at the end of the day.

1           I mean, those are the two choices, in  
2 fact. Either way, you have to handle it in the  
3 analysis. What we certainly did not want to do, and  
4 we talked about it, would be to stratify to ensure  
5 sufficient numbers so that we could analyze  
6 independently patients with prior cardiac risk  
7 versus patients without because we knew that would  
8 blow the sample size through the ceiling again.

9           DR. HIRSCH: I'm sure you don't need  
10 reminding that the UGDP study didn't show  
11 significant results until about the fourth year, I  
12 think. That may not be rectifiable by numbers. I  
13 mean, if you have another model that there's an  
14 incubation period of whatever the effect is, it  
15 doesn't matter how many people you put in the study,  
16 you may have to wait four years to see it. It would  
17 be a shame to make a cutoff point of three or four  
18 years at this point, but perhaps an analysis at that  
19 point and an extension if needed.

20           DR. FURBERG: Dr. Hirsch, I think you  
21 have a very good point. There could be a lag time  
22 to benefit or harm if that is what we are dealing  
23 with. It's very common now in many of the big  
24 trials to extend follow-up in a lot of examples  
25 particularly from the NIH-sponsored programs. So, I

1 think that, we can deal with.

2 DR. FAICH: The only other comment I  
3 would make is you know it may well be that UGDP  
4 didn't see those events because it enrolled  
5 relatively younger new onset diabetics in the  
6 initial enrollment cohort. That was one of the  
7 reasons why we said we didn't want to do that. I  
8 would expect that there would be probably a  
9 relatively linear accumulation of cardiac events  
10 over time because of that in this kind of study.  
11 But you're right.

12 DR. HIRSCH: Well, it's a very important  
13 consideration.

14 DR. FAICH: The other thing is, is this  
15 biology? Are we really talking about an induction  
16 period or an incubation period or a latency period?  
17 And I think our answer is, we don't know the answer  
18 to that.

19 DR. HIRSCH: That's my point.

20 DR. FAICH: Sure.

21 DR. HIRSCH: Therefore, the  
22 interpretation of the one-year data that we have,  
23 it's almost impossible to interpret them in any way.

24 DR. ILLINGWORTH: Yes, a couple of  
25 questions. One is, I wonder why you didn't consider

1 including troglidazone instead of insulin since you  
2 basically have three regimens that are going to  
3 raise insulin levels? Hyperinsulinism itself may be  
4 a risk factor and troglidazone would potentially  
5 give you a positive control looking at that other  
6 mechanism.

7 DR. FAICH: Yes.

8 DR. ILLINGWORTH: And the second  
9 question concerns stratification for lipid lowering  
10 drugs based upon the data now of clear benefit from  
11 treatment.

12 DR. FAICH: Right, right. Let me take  
13 the troglidazone, well, we did discuss it. One way  
14 to think about that would be at a fourth arm. I  
15 don't have to tell you what that does to both sample  
16 size and complexities of running it, and maybe loss  
17 of a potential augmenting therapy. So, that was one  
18 reason why we said no fourth arm.

19 The issue about insulin versus let's say  
20 troglidazone is historically we know that insulin  
21 from UGDP to some considerable degree is the  
22 question. In terms of being able to titrate down in  
23 dose, insulin probably -- if you have to make a  
24 choice between those two, has much to recommend it.  
25 Maybe the negative side of thinking about an insulin

1 arm is how will that affect patient recruitment on  
2 the front end? Will you then end up with a less  
3 than fully representative population? We did say we  
4 would want a pilot list to, in fact, look at that  
5 issue. That was the way the logic went on it.

6 DR. FURBERG: And regarding the lipids,  
7 I think you're right. There are other factors that  
8 will have to be considered also: treatment of blood  
9 pressure, aspirin and so on. I think the trial  
10 you're talking about would be on top of good medical  
11 treatment with assurances that you have balance  
12 between the groups.

13 DR. MOLITCH: Microalbuminurea is  
14 probably as important as cholesterol as a risk  
15 factor as well. But whether you treat that, we  
16 don't know makes any difference in cardiovascular  
17 disease. So, that's yet another unanswered  
18 question. My guess is that you're going to have so  
19 many variables that are going to be treated in so  
20 many different ways that you're going to end up like  
21 the UKPDS and not find anything at the end.

22 DR. CARA: You know, I can appreciate  
23 the time and effort that you put into designing a  
24 study like this, but my concern is somewhat similar  
25 to Dr. Molitch's in the sense that I don't know how

1 feasible a study like the one you described actually  
2 is. I mean, you're talking about a study that  
3 involves at least 5,000 to 6,000 patients assuming a  
4 dropout rate of somewhere between 30 to 40 percent.  
5 You'd have to recruit at least 10,000 patients for a  
6 study of this sort, and that's only with the three  
7 arms that you described. I don't see how feasible  
8 that actually is.

9 DR. FURBERG: Let me tell you that I'm  
10 involved with Women's Health Initiative, NIH  
11 sponsored, looking at three different interventions  
12 in a two by two by three factorial design. If  
13 you're looking at complexity, that is one when it  
14 comes both to enrolling and interpreting and dealing  
15 with that issue. I'm also involved in the NHLBI-  
16 sponsored ALLHAT study. Forty thousand patients  
17 with hypertension comparing four different regimens  
18 for treatment.

19 So, I think there is a collective wisdom  
20 and experience out there to deal with these issues.  
21 You're absolutely right. We need to be fully  
22 cognizant of the issues that you have raised and  
23 others, and be sure that at the end, we can  
24 interpret our findings.

25 DR. CARA: Well, I appreciate your

1        comments.  Thanks.

2                    My concern is whether the sponsor would  
3        want to commit to a study of that sort.  I mean,  
4        you're talking about studies that have been  
5        essentially proposed and supported by the  
6        government.  That's one thing.  Here, we're talking  
7        about something completely different.

8                    DR. FAICH:  Let me try to respond to  
9        that to the best of my ability and maybe turn it  
10       back to the sponsor.

11                   I think, as Dr. Furberg has pointed out,  
12        that one of the reasons why we can move into and  
13        it's something of a paradigm -- thinking about these  
14        very large trials is you also have to think about  
15        doing them not in phase III heavily monitored, 80-  
16        page, 100-page case report forms.  You really have  
17        to get down to the critical covariates and think  
18        about them as perhaps more of an epidemiologic  
19        undertaking.  There's randomization on the front  
20        end.  There's no question you're assigning therapy,  
21        so that makes them a trial.  But they have a  
22        different flavor in their aconda.  We did, by the  
23        way, power the study allowing for a 20 percent  
24        dropout per year.  That was yet another reason why  
25        we said there's no way this study can go on much

1 beyond three years. There will be few patients left  
2 and that was part of this kind of we took this at a  
3 realistic approach.

4 The other thing in terms of the cost of  
5 the study is, we don't think we're going to answer  
6 everybody's questions. I don't think we're going to  
7 answer the microalbuminurea question related to  
8 glucose control. This was very targeted toward the  
9 endpoints that we mentioned. While there are 100  
10 other natural history questions that one would love  
11 to answer, each time you start doing that, that's  
12 where the price really starts to go up as well. So,  
13 that was the other issue. We think that this is  
14 actually cost feasible and we did some preliminary  
15 costing on it. Again, I can't speak for the sponsor  
16 around that issue.

17 ACTING CHAIRMAN SHERWIN: Dr. Critchlow?

18 DR. CRITCHLOW: Well, clearly, the  
19 feasibility has something to do with whether you  
20 think the relative risk is somewhere in the nature  
21 of 1.1 as you said your meta-analysis might have  
22 shown versus the 1.5 to 2 full risk that we saw  
23 based on the preliminary data.

24 A couple of questions. On the current  
25 safety data -- I know the numbers are small but is

1       there any evidence that the risk varies by whether  
2       or not there was previous cardiovascular disease?  
3       Was it essentially comparable, two-fold increase,  
4       among those with and without disease or did that  
5       vary?

6                   DR. FAICH:  John Whisnant showed that,  
7       that if you have prior cardiovascular disease, that  
8       in and of itself increases your risks some  
9       threefold, not surprisingly.

10                  DR. CRITCHLOW:  Okay, so the difference  
11       between the repaglinide versus whichever was three  
12       or four fold among those with -- cardiovascular  
13       disease?

14                  DR. FAICH:  Oh, no, that was in the  
15       unadjusted analysis which you saw --

16                  DR. CRITCHLOW:  No, but if you  
17       stratified by previous cardiovascular disease, what  
18       was the relative risk in each of those, among those  
19       with prior disease and then among those without  
20       prior disease?

21                  DR. FAICH:  Oh, yes.  The numbers go  
22       away.  You can only do that in a multivariate  
23       approach.  That's where you saw the curve that was  
24       higher --

25                  DR. CRITCHLOW:  I saw the adjusted --

1 DR. FAICH: -- then come down to be  
2 comparable to glipizide.

3 DR. CRITCHLOW: I mean, I would think  
4 it's relevant whether or not they had prior disease  
5 or not. I guess there's no data to assess at this  
6 point, whether the risks would vary --

7 DR. FAICH: Yes, the one study that's  
8 critical in that regard was 049. John, you'll  
9 recall, showed the data of the imbalance in the  
10 randomization relative to prior cardiac disease.  
11 But going beyond that, the numbers just disappear  
12 and you really don't have much of an analytic  
13 opportunity.

14 DR. CRITCHLOW: So, in the current  
15 study, you powered it to do whatever, your stopping  
16 rule is based on what? That if you see something in  
17 excess of 1.5 or --

18 DR. FAICH: We didn't work through all  
19 the stop rules. It's clear that you have to allow  
20 for a wider confidence limit early-on. Then as you  
21 get more and more power, you narrow that down and  
22 that's not unprecedented. So, I don't know what  
23 that first year would be and it is risky, obviously,  
24 because you don't want to stop the study prematurely  
25 at the same time you want to discharge the ethical

1 responsibility. It's probably two or greater than  
2 two at year one for the relative risk stop rule  
3 issue, and then it would begin to decline after  
4 that. Bob Makish, actually, has had a lot of  
5 experience with that and brought that to our  
6 discussions.

7 I would point out again, to some extent,  
8 this is a work-in-progress and I'm presenting it --

9 DR. CRITCHLOW: No, I understand that.

10 DR. FAICH: -- conceptually.

11 DR. CRITCHLOW: And your total projected  
12 incidence rate of disease is on the nature of what,  
13 ten percent?

14 DR. FAICH: Well, no, it's actually  
15 more.

16 DR. CRITCHLOW: It's four percent per  
17 year.

18 DR. FAICH: We're estimating four  
19 percent a year so it's more like 12 percent, and  
20 then you have the dropout. So, it is ten percent.  
21 That gets you 200 events in each arm. So, you know,  
22 we reckon we'd have a lot of power, relatively  
23 speaking, including to allow us to do some  
24 stratification.

25 ACTING CHAIRMAN SHERWIN: Dr. Kreisberg?

1 DR. KREISBERG: Did your committee  
2 consider the possibility that there would be  
3 confounding factors associated with therapy? That  
4 is, improvement of glycemic control in the  
5 hemoglobin A<sub>1c</sub> potentially reducing the risk in the  
6 drug or a drug, potentially increasing the risk?

7 DR. FAICH: Yes, I think that's  
8 absolutely right. That is the most difficult thing  
9 about designing the study. You have a choice. You  
10 can try to push everybody to a targeted control  
11 level that actually means central laboratory. It  
12 means a lot of feedback. It means a lot of work at  
13 the patient/doctor level. So, that implies a lot  
14 of cost as well, to say nothing of whether you can  
15 really achieve it or not. Or you can, in fact, say  
16 no, we'll give those proposed targets and we'll  
17 analyze that, recognizing it may well be a  
18 confounder for the outcomes of interest. But it's a  
19 confounder you probably can analyze for to some  
20 extent. I would say that from a design and analytic  
21 viewpoint, that's the toughest issue in the whole  
22 study, without question.

23 DR. CARA: But you would really have to  
24 do some form of dose escalation study with some  
25 target endpoints because otherwise, you really can't

1 evaluate the potential risks and the potential  
2 benefits.

3 DR. FAICH: I agree. We would handle  
4 that probably by putting that in the protocol of  
5 suggesting when therapy changes, et cetera, within  
6 certain limits. See, the issue isn't whether you  
7 can provide that guidance. It's how much you  
8 enforce it in terms of the cost of the study and  
9 what you're doing.

10 The other way to answer that question to  
11 some extent is, is this to answer a biologic  
12 question or a actual care question? Is this a study  
13 of effectiveness or idealized efficacy? I mean, one  
14 issue is if you start to push it very hard in terms  
15 of protocol driven study in terms of the outcomes,  
16 you answer a better scientific question but it may  
17 be less generalizable. Then there's a dilemma in  
18 that as you'll recognize as well.

19 DR. CARA: But you didn't mention  
20 safety --

21 DR. FAICH: Well, we would collect  
22 adverse events. We would collect all SAEs, of  
23 course, and follow up on them appropriately, submit  
24 them appropriately and the like.

25 ACTING CHAIRMAN SHERWIN: Just a quicky.

1 Your choice of glipizide, was that based on the  
2 frequency of -- the reason I bring it up at all is  
3 in your preliminary data, you had very few patients  
4 on glipizide and they seemed to do worse than the  
5 drug. Whereas, you have a lot more data with  
6 glyburide and they seem to have less events. So,  
7 you know, it just seemed to me that the logical  
8 choice would have been glyburide.

9 DR. FAICH: Yes, I would say we talked  
10 about it. John wants to go ahead.

11 DR. WHISNANT: I wouldn't conclude from  
12 the earlier data that --

13 ACTING CHAIRMAN SHERWIN: No, there were  
14 not enough patients to say anything. No, I  
15 understand that.

16 DR. WHISNANT: And at least from our  
17 perspective as a diabetes company, glucatrol XL,  
18 glipizide, long-acting glipizide in this country is  
19 the largest, most available therapy. It is also  
20 pharmacokinetically the most different drug. So, if  
21 we're looking at a hypothesis that our therapy is  
22 new and that this dosing PK mode needs longer term  
23 testing, then that gives us the maximum delta  
24 difference in looking at that hypothesis.

25 ACTING CHAIRMAN SHERWIN: Okay.

1 DR. CARA: I might be asking you the \$20  
2 million question here. I don't know. Given the  
3 fact that typically, phase IV studies are fairly  
4 poorly monitored and poorly controlled, are you  
5 proposing that these studies be done prior to  
6 approval of the drug?

7 DR. FAICH: No, that is the \$20 million  
8 question. No, this is designed and proposed as a  
9 post-market -- I think you probably feasibly  
10 couldn't do this under IND rules. I think there  
11 needs to be a study done with some rigor. I think  
12 it has to be done in a credible manner, but I don't  
13 think you can talk about monitoring each site and  
14 validating each data bit. One would want to think  
15 about doing that on a sampling basis, looking for  
16 systemic error and the like. That's yet another  
17 reason why I would see this as a post-marketing  
18 strategy.

19 DR. CARA: I mean, do you think in all  
20 honesty that a study of this sort could be done as a  
21 phase IV?

22 DR. FAICH: Oh, I absolutely think it  
23 can. You know, actually, Richard Pieto and other  
24 people have talked about when you think about  
25 feasibility criteria for these kinds of studies. It

1 has to be relatively common disease. Therapy has to  
2 be relatively easy to apply. You can't have complex  
3 diagnostic requirements. The outcomes have to be  
4 objective and hard. You have to be able to have  
5 sufficient power and so on. I think this study fits  
6 that. I think that this is very much a feasible  
7 study.

8                   Again, I think one has to approach it  
9 quite differently than the usual phase III study.  
10 That's why, for some of us, this is -- I mean, there  
11 are challenges at many levels but some of that is  
12 philosophical change as well in terms of how to  
13 approach these trials.

14                   DR. MOLITCH: I'll just say one more  
15 time for the record that I think that in a study, if  
16 it's going to be as loose as you make it sound to be  
17 with the major focus being on the drug, that is  
18 probably of five risk factors for cardiovascular  
19 disease. It's the fifth one on the list that will  
20 actually affect cardiovascular disease -- after LDL  
21 cholesterol, after microalbuminuria, after glycemic  
22 control, after blood pressure control and the type  
23 of blood pressure control, that this three drug  
24 analysis is at the bottom of that list as the thing  
25 that will affect cardiac outcome.

1                   So, my guess is that we're really not  
2 going to see anything here because of all the other  
3 more powerful, confounding events. I would suggest  
4 that this study not be done in this design.

5                   DR. FURBERG: I'm part of another large  
6 NHLBI-sponsored study, a part of -- health study.  
7 It's a study looking at risk factors of coronary  
8 heart disease and stroke and they are really  
9 something that takes on more of a meaning as you get  
10 some gray hair.

11                   In that study, the two strongest  
12 predictors of cardiovascular events are hypertension  
13 and that is lipids lose their predictive power at a  
14 certain age. It's much less. So, the important  
15 thing according to our data is to deal with those.  
16 The trial will deal with the glycemia, diabetes, and  
17 the hypertension we need to control. I think in  
18 addition, we may want to add in some other factors  
19 but I don't think it's number five in the age groups  
20 that we are looking at, the old.

21                   DR. MOLITCH: Doing that 45 and older?

22                   DR. FURBERG: Well, that is still under  
23 discussion. My recommendation is that we go up to  
24 at least 55. That's where the events are. If you  
25 really want to do a study and get events, you don't

1 start off at 45.

2 DR. MOLITCH: That was your design. I'm  
3 sorry.

4 DR. FURBERG: Well, it's one that's  
5 proposed. We haven't discussed all the issues, but  
6 at least that's one issue I agree with you on. Go  
7 up in age and get the events up and focus on the two  
8 most important risk factors.

9 DR. NEW: Are you going to use both men  
10 and women?

11 DR. FURBERG: Absolutely.

12 DR. NEW: Then how will you control for  
13 estrogen use and the cardiovascular risk -- pardon?

14 DR. MOLITCH: Or raloxifine.

15 DR. NEW: Well, that's marvelous. But  
16 in the meantime, I think that's --

17 DR. FURBERG: I don't know whether it's  
18 coincidence or not, but I'm involved in another  
19 study, the HER Study, hormone, estrogen replacement  
20 study. We're going to have results first half of  
21 next year. I think that would guide us as to how to  
22 deal with that issue.

23 ACTING CHAIRMAN SHERWIN: Okay.

24 DR. FAICH: I can't help it. I just  
25 would add one other thing.

1                   ACTING CHAIRMAN SHERWIN: I can't stop  
2 this Committee.

3                   Roger, go ahead.

4                   DR. FAICH: Obviously, all the risk  
5 factors you can, and should, and need to collect at  
6 baseline. So, that's one part of the answer. The  
7 other part of the answer is that in this kind of  
8 study, I certainly think you have to, in fact,  
9 collect data on medications used. So, you have the  
10 opportunity to enter that into the analysis.

11                   By the way, I would do that as opposed  
12 to measuring blood pressures because it seems to me  
13 that medications as indicators, in many cases, are a  
14 more accurate measure. Because once you have to  
15 start specifying how you measure other clinical  
16 variables, which is not to say that they're not  
17 important, the feasibility does get compromised.  
18 Thank you.

19                   John, I should probably turn it back to  
20 you to wrap --

21                   DR. WHISNANT: Roger?

22                   DR. ILLINGWORTH: Just one question  
23 concerning the lipid stratification, just based on  
24 the data we have available and NZPT guidelines.  
25 Presuming you're going to have an upper level of LDL

1 in which you can not be ethically untreated?

2 DR. FURBERG: I agree with that  
3 wholeheartedly.

4 ACTING CHAIRMAN SHERWIN: Okay.

5 DR. FAICH: I'll turn it back to you,  
6 John. Do you have a closing comment?

7 DR. FLEMING: Dr. Sherwin.

8 DR. FAICH: Dr. Sherwin, you have it.

9 ACTING CHAIRMAN SHERWIN: I just wonder,  
10 do we need to go to number five or can we skip  
11 number five?

12 DR. FLEMING: I think the point of  
13 number five would be to allow the company to very  
14 quickly --

15 ACTING CHAIRMAN SHERWIN: Okay.

16 DR. FLEMING: -- summarize their hard  
17 findings and to give us an understanding of studies  
18 that are currently in progress or immediately  
19 anticipated starting.

20 DR. WHISNANT: I take the signal that we  
21 want this to be brief.

22 ACTING CHAIRMAN SHERWIN: Very brief.

23 DR. WHISNANT: Let's see if I can rise  
24 to that challenge.

25 ACTING CHAIRMAN SHERWIN: Okay.

1 DR. WHISNANT: I should speak into a  
2 microphone for the reporter in the back.

3 Novo Nordisk has submitted an NDA which  
4 has been reviewed. We believe the NDA includes more  
5 than an adequate basis demonstrating efficacy of  
6 this drug in the treatment of type 2 diabetes  
7 mellitus.

8 We believe that the safety profile of  
9 this drug has been demonstrated both by a safety  
10 margin of dose and by exposure of 1,228 patients  
11 over a year's trial -- actually 834 patients, fully  
12 exposed for more than a year. We believe there's an  
13 adequate representation of patients in that database  
14 in order to assure the safety of this product.

15 Because of a number of cardiovascular  
16 events in one trial which we believe has some  
17 considerable question about randomization bias,  
18 we've made a major commitment to at least propose  
19 for your consideration on a post-approval basis,  
20 that we will carry out a study that will include not  
21 only cardiovascular risk monitoring, but will teach  
22 us more about the use of a different kind of  
23 secretagogue therapy versus, I must admit, our  
24 insulin in a comparator long-term trial.

25 There are a number of questions which

1 remain unanswered. We are not asking for an  
2 indication which addresses the natural history  
3 question, but we believe that our long-term  
4 comparator trial will assist in generating that  
5 information. We are not asking for indications of  
6 combination therapy except for combination with the  
7 drug that we've demonstrated a significant benefit  
8 with, that is metformin. We believe within these  
9 limitations that this new product should be added to  
10 the armamentarium available for treatment of  
11 patients with type 2 diabetes.

12 I will be happy to answer any remaining  
13 questions. I have some slides to indicate what our  
14 continuing program of studies is relative to the  
15 combination of this drug with a diene with regard to  
16 a purpose design study to get more data regarding  
17 the use of this drug relative to an advantage of  
18 hypoglycemia severity, frequency, and relationship  
19 to dose. That study is also well along in its  
20 design phase and ready to implement as soon as the  
21 Agency gives us the go ahead.

22 We thank you very much. I'll be happy  
23 to address any further questions.

24 ACTING CHAIRMAN SHERWIN: Okay. The  
25 group is suddenly silent. That's terrific. Okay.

1                   Okay, I think we're about ready to  
2                   address the four questions that are posed to us.  
3                   We'll go around the room from my right to left and  
4                   then we'll go backwards. The first is, "are the  
5                   various study designs and efficacy endpoints  
6                   adequate to assess the effectiveness and safety of  
7                   this drug?" The various study designs that have  
8                   already been produced.

9                   Joe?

10                  DR. HIRSCH: Well, let me just say as a  
11                  prelude to my answer, if I may, in one sentence or  
12                  two. This is an extremely interesting drug and a  
13                  very, very promising one. I would hope that some  
14                  further animal studies which haven't been done  
15                  utilizing genetically obese animals and animals  
16                  otherwise having pancreatic dysfunction would make  
17                  use of this fascinating drug to probe those  
18                  abnormalities.

19                  My answer to one is going to sound  
20                  awfully bad, but it's a very hardy no. I do not  
21                  feel that the designs and efficacy endpoints are  
22                  adequate to assess the effectiveness and safety of  
23                  the drug. My specific reason for that is that we  
24                  haven't seen clear studies as to how, in fact, the  
25                  drug would be used. I assume it will have to be

1 used in much higher dose or with other drugs to be  
2 fully clinically effective. There are not adequate  
3 studies in my mind of that to permit me to say that  
4 this is now -- I now understand all the ins and outs  
5 of the efficacy and effectiveness and safety of the  
6 drug, et cetera. So, my answer is no.

7 ACTING CHAIRMAN SHERWIN: Mark?

8 DR. MOLITCH: My answer is yes. I think  
9 we have sufficient data to show that it is as  
10 effective as other sulfonylureas and is at least as  
11 safe. You're right. We don't know all the ins and  
12 outs of this and I think a lot of those still need  
13 to be learned. But I think at this point, it does  
14 fit all those criteria.

15 ACTING CHAIRMAN SHERWIN: Roger?

16 DR. ILLINGWORTH: I would say yes. I  
17 think the efficacy data that Dr. Fleming described  
18 has been demonstrated in placebo control trials and  
19 comparative trials. I would echo my colleague's  
20 comments that we clearly need more data about the  
21 use of this drug in combination therapy with other  
22 oral agents. I think we also need to look at  
23 potential drug interactions with Asians that haven't  
24 been looked at. Things, in particular, that go with  
25 the cytochrome P450 system in the liver, how they're

1 going to increase the risk of being hypoglycemic if  
2 you're on erythromycin or something like that. But  
3 my answer is yes.

4 ACTING CHAIRMAN SHERWIN: Okay.  
5 Kathleen will read Dr. Marcus'.

6 MS. REEDY: Dr. Marcus says yes but only  
7 if the question is specifically whether this drug is  
8 as good as the comparator drugs that are already  
9 approved.

10 ACTING CHAIRMAN SHERWIN: José?

11 DR. CARA: My answer is yes, but echoing  
12 some of the comments that have been raised. That is  
13 that I think there are still a variety of questions  
14 that remain that will hopefully tap into the true  
15 potential of this drug. I think there are a variety  
16 of theoretical benefits to this drug that have been  
17 alluded to by the sponsor and by other members that  
18 are here. Unfortunately, they have not been borne  
19 out by some of the clinical data that's been  
20 presented and I'm hopeful that additional studies  
21 will really address some of those issues.

22 I think the safety issues are still a  
23 question. The data that's been presented so far  
24 certainly show that the drug is no worse than  
25 currently available therapy, but I've got to really

1 make a point about the fact that these are very  
2 short-term studies in what is a very chronic type of  
3 disease. I hope that the sponsor will agree to and  
4 will, in fact, carry out some additional studies,  
5 longer-term studies that will address some of the  
6 safety issues that have been raised.

7 DR. CRITCHLOW: Well, I say yes and  
8 seconding the comments of Dr. Molitch and Marcus and  
9 Cara. Just one additional comment is the efficacy  
10 data, again, are not consistent with what might be  
11 heralded as a breakthrough in terms of the action of  
12 the drug. It's clearly no better than what's out  
13 there.

14 ACTING CHAIRMAN SHERWIN: I'll vote yes  
15 as well, even though it's I believe barely adequate.  
16 But if I have to say between yes and no, I would  
17 come down at yes even though I think all of the  
18 Committee has serious concerns about safety issues  
19 and the lack of the full profile of its efficacy.

20 DR. KREISBERG: I'd like to compliment  
21 the sponsor on maintaining their composure during  
22 all this badgering. It's been fairly remarkable to  
23 me that you could stay in such good humor.

24 I vote yes. My comment is that it is  
25 probably as good as, but I have not seen any

1 evidence that it's any better than the sulfonylureas  
2 and it's probably as safe. I think it's a very  
3 interesting and exciting and new drug. If the  
4 sponsor follows through on all of the suggestions  
5 that have been made, that we ought to know a lot  
6 more about it the next time around. I think that  
7 that would be very gratifying.

8           The one thing that continues to bother  
9 me -- and I guess doctors will be doctors and that's  
10 why it bothers me -- is that the naive patients seem  
11 to be more susceptible to the hypoglycemic effects  
12 of the drug. I would hope that the labeling would  
13 carry some clear instructions on how to utilize this  
14 drug, particularly in those types of patients.

15           ACTING CHAIRMAN SHERWIN: Maria?

16           DR. NEW: I'm having trouble deciding  
17 how to vote and have finally decided I'll vote this  
18 way. I think it's yes on the basis of the short-  
19 term data which have been presented. The drug is as  
20 at least as good as any of the other glucose  
21 lowering drugs.

22           The long-term data that's been presented  
23 to me -- after all, diabetes is not something you're  
24 going to treat short-term -- I find that the  
25 clinical studies don't address the actual practical

1 practice of a diabetologist in regulating glucose  
2 control because the annual study -- those were the  
3 slides I wanted to show -- did not indicate to me  
4 that there was any benefit at the end of 12 months.  
5 Now, I don't know whether there will be benefit at  
6 the end of two or three years, so I really have a  
7 bifid vote.

8 ACTING CHAIRMAN SHERWIN: Is there such  
9 a thing as a bifid vote?

10 DR. KREISBERG: If you're a pediatric  
11 endocrinologist there is.

12 ACTING CHAIRMAN SHERWIN: So, we've got  
13 a half-a-vote on either side, is that it?

14 DR. NEW: Yes.

15 ACTING CHAIRMAN SHERWIN: Yes, okay.

16 Okay, the next question is "are there  
17 any issues specifically related to the use of the  
18 short-acting preprandial oral therapy that have not  
19 been addressed by the sponsor?"

20 Maria?

21 DR. NEW: No. In fact, I think that's  
22 the most exciting and valuable aspect of this new  
23 drug which is that I'm convinced on the basis of  
24 data that taking the drug before the start of meals  
25 does improve the glucose control post-prandially. I

1 think they've done this study very well.

2 DR. KREISBERG: Well, I would agree with  
3 that. I think it's an exciting new concept. I  
4 would like for the sponsor to develop more  
5 information on the marked discordancy or variability  
6 between plasma levels of the drug and the acute  
7 response in terms of glucose disappearance, and to  
8 look into issues that have to do with nutrient drug  
9 interactions. Because we didn't talk about that,  
10 but I think that's a potentially important problem  
11 in things relating to the bioavailability of the  
12 drug.

13 ACTING CHAIRMAN SHERWIN: Okay. Any  
14 issues that have not been addressed?

15 Yes, I would like to see free levels of  
16 the drug measured so I could better interpret the  
17 results. I would urge the sponsor to develop an  
18 assay if at all possible, put effort into that.

19 I'd also feel that the kinetics of the  
20 drug, in terms of its biological action, have not  
21 been adequately answered. I believe that measuring  
22 insulin levels with differing glucose levels makes  
23 it uninterpretable to me to figure out what the  
24 duration of action is. That's critical. Although  
25 the drug levels are impressively up and down, I

1 still don't know about the biology, kinetics of the  
2 biological response. So, I think that some  
3 fundamental studies should be done at least in  
4 animals. If not, it could be done in humans to look  
5 at this.

6 DR. CRITCHLOW: I agree with Dr.  
7 Sherwin.

8 DR. CARA: I think there are several  
9 issues that really need to be addressed, or at least  
10 that I would like to see addressed. One of the  
11 principal ones relates to mechanism of action. It  
12 seems that we've got just a black box where Prandin  
13 does something that we can evaluate clinically, but  
14 we have a very little insight into what's actually  
15 within that big, black box. Finding what's in there  
16 I think would be very important, especially in terms  
17 of evaluating efficacy and perhaps drug combinations  
18 or alternative therapies that may work better.

19 What I would like to see is also some  
20 sort of dose escalation study. I feel like even  
21 though the sponsor did a fairly good job of  
22 presenting efficacy data, I would have liked to have  
23 known what that baby could do in terms of really  
24 using optimal doses to get optimal effect. I don't  
25 think that was actually done in many of the studies

1 that were described by the sponsor. So, I think  
2 having more legitimate targets of efficacy and  
3 pushing the drug a little bit would make a lot of  
4 sense.

5 I'd like to see some data on convenience  
6 and some of the issues that were addressed before in  
7 terms of whether this is really as convenient as we  
8 think it is. My impression is that it probably will  
9 be, but it would be nice to have corroboration of  
10 that impression.

11 Those are my major questions, if you  
12 will, that I'd like to see the sponsor take on.

13 ACTING CHAIRMAN SHERWIN: Roger?

14 Oh, what did Dr. Marcus do?

15 MS. REEDY: Okay, Bob Marcus. Thorough  
16 analysis of lipoprotein changes, both fasting and  
17 post-prandial. True incidence of hypoglycemia  
18 measured blood glucose based on average and  
19 variation on FPG on therapy.

20 ACTING CHAIRMAN SHERWIN: So the answer  
21 is yes?

22 MS. REEDY: That's are there any issues?

23 ACTING CHAIRMAN SHERWIN: Yes, the  
24 answer is yes. Yes.

25 DR. ILLINGWORTH: Yes, I would echo the

1 utility looking at post-prandial lipemia as a  
2 potential beneficial effect. I think I'd also like  
3 to see some other patient populations looked at.  
4 The drug is bound to albumen. Patients with  
5 diabetes frequently develop nephrotic syndrome.  
6 What about patients with nephrotic syndrome? Is the  
7 pharmacokinetics the same?

8 Then finally, just looking more at  
9 drug/drug interactions within the intestinal tract.  
10 Do things that delay gastric emptying affect the  
11 absorption? We know about cimetidine. What about  
12 some of the other proton pump inhibitors? Do they  
13 affect absorption?

14 DR. MOLITCH: I think the answer is yes.  
15 I think there is a major shortfall here on the part  
16 of the sponsor as far as trying to really capitalize  
17 on this short acting drug. I don't know how fasting  
18 blood sugar levels are decreased with this drug. I  
19 don't know what's happening to hepatic glucose  
20 output. I haven't seen any clamp studies looking at  
21 glucose production versus glucose disposal. I'm  
22 trying to figure out what's going on first thing in  
23 the morning here.

24 I haven't seen them capitalize on this  
25 short acting drug to increase insulin secretion

1 acutely controlling post-prandial blood sugar levels  
2 and then using that in combination with a longer  
3 acting agent overnight or using it with an injection  
4 of insulin overnight which might be a really very,  
5 very nice combination of therapy. I think that  
6 those things really should be done to help exploit  
7 the benefits that this drug might give us.

8 I'm concerned, as I mentioned  
9 previously, about patients who do have decreasing  
10 clearance. I thought I detected a buildup of drug.  
11 Given the large variability that we have seen before  
12 in the area under the curve with the dosing, that we  
13 need much more data on that to be able to say that  
14 we really can use it in patients who have decreased  
15 clearance. I would not approve the drug for use in  
16 patients with decreased renal function at this point  
17 in time until we have such data in addition to not  
18 using it in the patients with hepatic disease.

19 So, I think that a lot of work needs to  
20 be done in this area. I think that work will prove  
21 of great benefit to the sponsor for expanded use of  
22 this drug.

23 ACTING CHAIRMAN SHERWIN: Jules?

24 DR. HIRSCH: I'm not sure we know the  
25 right dose. I'm not sure I know the best

1 combination if it's to be used with something else.  
2 I don't know the relationship to spontaneous  
3 hypoglycemia and all the other things. So, my  
4 answer is yes.

5 ACTING CHAIRMAN SHERWIN: Another point  
6 that I forgot to mention is that the trials really  
7 were biased against numbers of minorities. We  
8 should be sure that all the various minorities that  
9 are represented in the US are adequately studied to  
10 look at the risk benefit ratio in those populations.

11 Okay. Number three: "Is the excess in  
12 cardiac events reported for Prandin-treated patients  
13 compared to those treated with other therapies  
14 significant. If so, how should this issue be  
15 resolved?"

16 DR. HIRSCH: Didn't we just deal with  
17 that?

18 ACTING CHAIRMAN SHERWIN: We did.

19 DR. HIRSCH: Well, we'll start here.  
20 The answer to that is I don't know. I would hope  
21 that if it ever is marketed, we'd find out. Many of  
22 these questions are sort of ambiguously worded, you  
23 now? I don't know what addressed by the sponsor  
24 means, et cetera. My answer to this is I don't  
25 know.

1 DR. MOLITCH: I'm not worried about the  
2 excess in the cardiac events in this particular drug  
3 compared to other drugs. Nor am I particularly  
4 worried about hypoglycemia which, to me, is not a  
5 big deal in patients with type 2 diabetes that I  
6 treat with sulfonylureas. It's just not a major  
7 problem for me with these patients. I think that  
8 the study that was outlined to address the  
9 cardiovascular issues is going to be an Emperor's  
10 New Clothes where we're going to spend millions and  
11 millions of dollars, pretend that we know what we're  
12 doing and not get an answer.

13 DR. HIRSCH: So, what is it, yes or no?

14 DR. MOLITCH: I'm not concerned about  
15 it.

16 ACTING CHAIRMAN SHERWIN: So, the answer  
17 is --

18 MS. REEDY: No. It's not significant.

19 ACTING CHAIRMAN SHERWIN: Correct.

20 DR. ILLINGWORTH: My answer would also  
21 be no. It's a higher risk patient population. Just  
22 looking at the cardiovascular events that occurred,  
23 there wasn't anyone that predominated or that  
24 suggested a red flag for patients with a history of  
25 a certain arrhythmia or on certain other agents.

1 I think it would be worthwhile  
2 monitoring in any post-marketing surveys, is there  
3 any particular patient group who is at higher risk  
4 for developing some kind of arrhythmia or --  
5 population in something like that. I think the data  
6 available -- I'd say no.

7 ACTING CHAIRMAN SHERWIN: Dr. Marcus?

8 MS. REEDY: Dr. Marcus says no. "Post-  
9 marketing phase IV follow-up study is needed. The  
10 proposed study seems reasonable but would prefer to  
11 see a mechanism to add metformin for patients who do  
12 not respond adequately to the assigned study drug  
13 alone. Without that, there may be a problem with  
14 retention of subjects for three years."

15 He already expressed that to you.

16 DR. CARA: I think there are issues that  
17 suggest that the cardiac risks and other potential  
18 side effects may be significant. I think what's  
19 going to happen as this drug becomes available --  
20 presumably, it will be although we'll obviously see  
21 that in just a little bit -- I think people will  
22 start using it fairly liberally. It's a fairly  
23 decent drug and I think that people will start using  
24 it for different sorts of populations. I think that  
25 having a better sense of what the potential risks

1 and benefits are is important.

2                   Unfortunately, I don't think that a  
3 phase IV study is the way to go about doing that. I  
4 think it will only be the test of time that will  
5 really tell us about the long-term efficacy and  
6 safety of this drug.

7                   DR. CRITCHLOW: The excess may be  
8 significant. I don't think there's anyway based on  
9 the data we have to adequately address that. I also  
10 agree with Dr. Cara that without additional exposure  
11 data, that would be the only way we would get that  
12 information.

13                   MS. REEDY: Is that a yes?

14                   DR. CRITCHLOW: Yes.

15                   ACTING CHAIRMAN SHERWIN: I have no idea  
16 based upon the data. I mean, it depends also on the  
17 comparitors. But you know, we just don't have  
18 enough data, I don't think, to answer yes or no to  
19 that question. I definitely think if the drug is  
20 released that a careful study should be done  
21 regarding cardiovascular risk. Then the other issue  
22 is given the fact that we don't know about the risk,  
23 should we have anything -- you know, an insert  
24 regarding the potential risk since it is not  
25 established at this time, whether patients with a

1 history of cardiovascular problems should use the  
2 drug with caution.

3 DR. KREISBERG: That means no diabetic  
4 will get it.

5 ACTING CHAIRMAN SHERWIN: Well, no, no.  
6 No, that's not what I said. I'm talking about  
7 people who have had a previous MI who are currently  
8 being treated for arrhythmia. All patients with  
9 type 2 diabetes have a higher risk of cardiovascular  
10 disease, but then there's a subgroup of patients who  
11 have active ongoing cardiac risk that's significant.  
12 I think in that group of patients, given the lack of  
13 knowledge and the preliminary data that we have,  
14 that we should be a little bit cautious in terms of  
15 the prescribing community.

16 DR. KREISBERG: Okay. I'd like to  
17 answer that I also don't know. I'm not sure that  
18 the trial that has been described will be  
19 successful. I do think that it's important to keep  
20 track of all of the adverse events that occur with  
21 this drug. As best I can tell, I can't see that the  
22 risk with this drug is any greater than it is with  
23 any of the other sulfonylureas, and I don't think it  
24 should receive preferential labeling.

25 DR. MOLITCH: Your answer is no then?

1 DR. KREISBERG: My answer is I don't  
2 know.

3 MS. REEDY: I don't know. I have a  
4 special category for those.

5 DR. NEW: My answer is probably no  
6 because there isn't a significant difference from  
7 other drugs, but it's very difficult for me to  
8 decide.

9 I would recommend that rather than this  
10 elaborate study, that a careful post-marketing  
11 monitoring study be done in which complications over  
12 time are reported and tabulated, and then a  
13 reassessment made.

14 ACTING CHAIRMAN SHERWIN: Okay. Now, we  
15 get to the final. Based on the efficacy and safety  
16 data presented and your assessment of the overall  
17 benefits compared to the risk of Prandin therapy, do  
18 you recommend that this drug be approved for  
19 marketing?

20 DR. NEW: My answer is yes. I say yes  
21 because I don't want to deprive my patients and my  
22 family members of type 2 diabetes on an excellent,  
23 short, rapid-acting drug. I think that this drug,  
24 even if used short-term, has been shown to be  
25 efficacious. As I said in my previous vote, I don't

1 see much difference from the complications of other  
2 glucose-lowering drugs.

3 DR. KREISBERG: My answer is yes and  
4 with the same proviso that I think the sponsor  
5 develop some clear guidelines for physicians on how  
6 to use it.

7 ACTING CHAIRMAN SHERWIN: I will vote  
8 yes also, even though I have a lot of concerns about  
9 all the problems we've discussed, particularly the  
10 numbers of patients studied who were virgin, naive  
11 patients. I think that we need to have more  
12 information on that group of patients.

13 DR. CRITCHLOW: I also say yes,  
14 basically because it is not significantly worse than  
15 what is out there.

16 DR. CARA: I vote yes, although I too  
17 have reservations. Unfortunately, I think it's only  
18 through approval of this drug, that at this time  
19 appears to be relatively safe and efficacious, that  
20 we will learn more about its long-term effects and  
21 its true safety and efficacy.

22 ACTING CHAIRMAN SHERWIN: Dr. Marcus?

23 MS. REEDY: Marcus says yes.

24 ACTING CHAIRMAN SHERWIN: Dr.  
25 Illingworth?

1 DR. ILLINGWORTH: My vote is also yes  
2 with the hope that they will conduct further studies  
3 looking at other hypoglycemic drugs in combination  
4 therapy to extend what's already been done.

5 ACTING CHAIRMAN SHERWIN: Dr. Molitch?

6 DR. MOLITCH: Yes.

7 ACTING CHAIRMAN SHERWIN: Dr. Hirsch?

8 DR. HIRSCH: No.

9 ACTING CHAIRMAN SHERWIN: Okay. Well,  
10 I'm glad they were not unanimous, you know, after  
11 this session.

12 So, the final vote on the last question  
13 is 8:1, obviously.

14 I'd like to thank the sponsor for their  
15 efforts today, the FDA, and all of you for spending  
16 the whole day with us, a day that we thought would  
17 end very quickly. Thank you.

18 MS. REEDY: I would like to ask the  
19 Committee to please take all of your materials with  
20 you. We are meeting in a different hotel tomorrow.  
21 Your blue folder contains tomorrow's agenda and  
22 questions, so please take the blue folder.

23 If you would like to leave your  
24 materials to be shredded, you may. We'll have  
25 somebody else pick that up.

1 (Whereupon, the meeting was concluded at  
2 4:28 p.m.)  
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