FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE MEETING

DAY TWO

Silver Spring, Maryland

Wednesday, July 2, 2008

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P R O C E E D I N GS

(8:01 a.m.)

DR. BURMAN: Good morning. Why don't we get started this morning? Let me welcome everybody to the second day of the FDA meeting.

Paul Tran will start with an announcement.

MR. TRAN: Good morning. My name is Paul Tran. I'm the designated federal official for today's meeting. I would like to remind everyone present to please silence your cell phone, BlackBerrys, and other devices if you have not already done so. I would like to identify the FDA press contact person, Ms. Susan Cruzan.

Please stand up. Thank you.

DR. BURMAN: As we did yesterday, we think it's important for everyone to reintroduce themselves. If we can go around the table, starting on this side, please.

DR. PAN: Good morning. I'm Gerald Dal Pan, director of the Office of Surveillance

and Epidemiology at CDER at FDA.

DR. TEMPLE: Bob Temple. I'm director of the Office of Medical Policy at FDA.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the director of the Office of New Drugs at FDA.

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

DR. PARKS: Mary Parks, director, Division of Metabolism and Endocrine Products.

DR. JOFFE: I'm Hylton Joffe, the lead medical officer for the Diabetes Drug Group at FDA.

DR. HOLMBOE: Eric Holmboe. I'm a general internist. I'm from the American Board of Internal Medicine.

DR. KONSTAM: Marv Konstam, cardiology, from Tufts University and NHLBI.

MR. LESAR: Timothy Lesar, director of Pharmacy Services at Albany Medical Center, Albany, New York.

MR. PROSCHAN: Mike Proshan. I'm a

statistician from NIAID.

MS. FLEGAL: Katherine Flegal from the Centers for Disease Control and Prevention.

MR. BERSOT: I'm Tom Bersot from the University of California, San Francisco.

MS. HENDERSON: Jessica Henderson. I'm the consumer representative, Western Oregon University.

DR. BURMAN: Ken Burman, head of endocrinology at the Washington Hospital Center and professor at the Department of Medicine, Georgetown University.

MR. TRAN: Paul Tran, the designated federal official for the EMDACS Advisory Committee.

DR. GOLDFINE: Allison Goldfine, head of clinical research at Johnson Diabetes Center, Boston.

MR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. FELNER: Eric Felner, pediatric

endocrinologist at Emory University in Atlanta.

MS. DAY: Ruth Day, director of the Medical Cognition Laboratory at Duke University.

DR. ROSEN: Clifford Rosen, endocrinologist, Maine Medical Center.

MS. KILLION: Rebecca Killion, patient representative, Bowie, Maryland.

DR. SAVAGE: Peter Savage, senior advisor to the director of the Diabetes Division at NIDDK.

DR. FRADKIN: Judy Fradkin, director of the Diabetes Division at NIDDK.

DR. VELTRI: Rick Veltri, industry representative, Schering-Plough Research Institute.

DR. BURMAN: Thank you very much and welcome. We have another announcement that I will read.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that

today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

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

A press conference will be held in the Potomac Room immediately following the meeting today. Also, the Committee is reminded to please refrain from discussing

the meeting topic during breaks or lunch.
Thank you.

Mr. Tran?

MR. TRAN: Hi, good morning. Paul Tran. I would like to read the Conflict of Interest Statement for this morning's meeting.

The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are Special Government Employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulation.

The following information on the status of the Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found in 18 U.S.C. 208 and 712 of the federal Food,

Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

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

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

Related to discussion of today's meeting, members and temporary voting members

of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for the purpose of 18 U.S.C. 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, Cooperative Research and Development Agreements; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussions of the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C.

208(b)(3) and 712 of the Food, Drug, and Cosmetic Act to Dr. Thomas Bersot.

Dr. Bersot owns stock in an affected firm worth between $25,001 and $50,000. Limited waivers have been issued in accordance to 18 U.S.C. 208(b)(3) and 712 of the Food, Drug, and Cosmetic Act to Drs. Robert Califf and Steven Nissen.

Drs. Califf and Nissen will not be allowed to participate in the Committee's discussions, deliberations, or vote in the matters coming before the Committee.

Dr. Califf's limited waiver is for his employer's two studies on affected product. His institute receives more than $300,000 per year for both studies. His employer has another study on an affected product that is currently under negotiation. Dr. Califf's waiver also covers his consulting job on an affected product for which he receives less than $10,000 per year, and another consulting job for an affected

firm for which he receives between $10,000 and $50,000 per year.

Dr. Nissen's limited waiver entails his employer's three studies on affected products. His institute receives between $100,001 and $300,000 per year for two studies, and more than $300,000 per year for one study.

FDA has also decided to limit Dr. Saul Genuth's participation due to his past and current involvement with the Action to Control Cardiovascular Complications of Diabetes -- ACCORD -- clinical trial.

Dr. Genuth will be allowed to participate in the Committee's discussions, deliberations, but will be excluded from any vote with respect to the discussions on the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

With regard to the FDA's guest

speakers, the Agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentations and/or comments made by the speakers.

Dr. David Nathan has acknowledged that he is the principal investigator for an investigator-initiated study funded by Sanofi-Aventis.

Dr. Hertzel Gerstein has acknowledged that he has research contracts with GlaxoSmithKline, Sanofi-Aventis, King, and Merck. He lectures for GlaxoSmithKline, Sanofi-Aventis, Eli Lilly, NovoNordisk, Merck, and Boehringer-Ingelheim. He's also a consultant for GlaxoSmithKline, Sanofi-Aventis, Eli Lilly, NovoNordisk, Merck, Boehringer-Ingelheim, Roche, and Medtronic.

Dr. Robert Ratner has acknowledged that he owns stocks in Merck, Johnson &

Johnson, and Abbott.

He has research contracts with AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck, NovoNordisk, Pfizer, and Takeda. Dr. Ratner also serves on advisory boards for Amylin, AstraZeneca, Eli Lilly, GlaxoSmithKline, NovoNordisk, Sanofi-Aventis, and Takeda.

Professor Rury Holman has acknowledged that he has educational grants from Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Novartis, NovoNordisk, and Pfizer. He lectures for Astellas, Bayer, Eli Lilly, GlaxoSmithKline, Merck, NovoNordisk, and Sanofi-Aventis.

Dr. Holman is also a scientific advisor to Amylin, Eli Lilly, GlaxoSmithKline, Merck and Novartis. Lastly, his employer is currently negotiating for studies of two affected products.

As guest speakers, Drs. Nathan, Gerstein, Ratner, and Professor Holman will

not participate in committee deliberations nor will they vote.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing these waivers are described in the wavier documents, which are posted on the FDA's internet website at www.fda.gov/ohrms/dockets/default.htm.

Copies of these waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 630 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Enrico Veltri is serving as the industry representative, acting on behalf of all regulated industry. Dr. Veltri is an employee of Schering-Plough.

We would like to remind members and

temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. BURMAN: Thank you. We will now proceed with the open public hearing. Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages

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

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this Committee in

their consideration of the issues before them.

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

One quick announcement, that there is, in addition to the speakers for the open public hearing, there is a written statement from the American Heart Association in your packet.

I believe Dr. Moses is the first speaker.

DR. MOSES: Thank you, Dr. Burman, members of the Committee, members of the FDA. I appreciate the opportunity to be able to address this group on such an important topic.

An obvious conflict of interest: I am a full-time employee of NovoNordisk, Incorporated, as well as having stock in that company.

As you can see from the slide, my name is Alan Moses. And I serve as the corporate vice president and global chief medical officer for NovoNordisk, the world's largest manufacturer of insulin.

For the last 85 years, NovoNordisk has worked to assure that patients around the world who suffer with diabetes have the highest-quality and most-innovative diabetes treatments available to improve their outcomes and to reduce both the individual and societal burden of diabetes.

Currently, NovoNordisk invests more on diabetes research than any entity in the world except for the United States government. These expenditures are directed toward improving available therapies for diabetes. NovoNordisk believes that new

treatments are critical to improve the likelihood and the safety of patients being able to achieve appropriate target levels of glucose control.

While multiple new therapies of different pharmacologic classes have been approved for diabetes treatment, major gaps still exist in the ability of patients to achieve target glucose control on a routine basis, as eloquently stated by Ms. Killion yesterday. Despite many new drugs, health care professionals and patients are faced with challenges of translating efficacious current therapeutic molecules into effective treatments.

At this meeting, we are discussing what constitutes appropriate endpoints for diabetes drug development and specifically the role of CBD markers or hard endpoints in drug approval and labeling. NovoNordisk believes strongly that glycemic control is measured by assessment of integrated blood

glucose, whether by HbA1c or mean blood glucose is the sine qua non of diabetes drug development. The data linking improved glycemic control to diabetes microvascular complications and to patient quality of life is irrefutable, and has been established by well-controlled, randomized clinical trials in both type 1 and type 2 diabetes.

Based on the discussion yesterday, we all are aware of the challenges posed by demonstrating an effective glycemic control on macrovascular complications. There is strong epidemiologic association between worsening glycemic control and increasing cardiovascular risk. And follow-up studies on intensive controls, such as the EDIC continuation of the DCCT study, have shown long-term beneficial cardiovascular effective of intensified glycemic control.

However, direct RCTs evaluating CV outcomes have not been as conclusive. Indeed, as was discussed yesterday, the

results of the recent ACCORD, VADT, HEART 2D, and advance studies point out the challenges of large-scale outcome studies designed to assess the role of glycemic control on cardiovascular endpoints and all-cause mortality in specific patient populations. This disappointment of not demonstrating a clear, statistically significant, positive effect of glucose control and the occurrence of MI, stroke, and overall cardiovascular mortality has stirred great controversy as to the value of intensifying diabetes therapy.

NovoNordisk believes that this concern is misplaced, as the relationship between glucose control and diabetes microvascular complications is reason enough to aggressively pursue glucose control as close to the normal range as can be safely achieved in the individual patient. Macrovascular and microvascular disease risk is multifactorial. In the case of the former, there's clear evidence from the

Steno-2 study, including its up to 13-year follow-up data and others, that multifactorial treatment of all vascular risk factors in diabetes, including hypertension, hyperlipidemia, smoking, aspirin use, and hyperglycemic can have a profound impact on microvascular and macrovascular complications, including mortality.

So how do we place CBD into the context of diabetes drug development and approval? The currently published data within diabetes are contradictive, but suggest that treatment of hyperglycemia is important to reduce the risk of CBD. NovoNordisk agrees with the prior stated position of the FDA, that specific requests for pre-approval, clinical cardiovascular outcomes data should be discussed if adverse CBD signals are detected in the preclinical or early clinical program.

Currently, required data on ECG, QT interval studies, and the biochemical CBD

markers are regarded as sufficient for assessing cardiovascular risks of any diabetic drugs in addition to the clinical trial safety assessment. NovoNordisk supports the idea that consensus guidelines on relevant combined laboratory and clinical and surrogate endpoints should be established, eventually by a standing committee of clinical experts, with representatives from the American Diabetes Association, Cardiovascular Associations, and industry.

We also recognize that specific markers may evolve as new biochemical and genetic markers are identified. Any major signals detected in pre-approval data that are linked to adverse CV outcomes or a meaningful increase in CV risk, will need to be examined in relevant studies, either in the pre-approval process or as post-approval commitments as agreed upon between the developer and the regulatory agency.

Depending on the nature of the signal, these trials could either be RCTs, observational trials, or registries best designed to address a specific issue.

There are two general issues that require additional discussion. First, does intensive glycemic control reduce the risk of adverse cardiovascular endpoints? As noted above, the answer to this question has become somewhat elusive.

Our understanding of the importance of the level of glucose control is complicated by the therapeutic strategy to achieve that control.

Further, differences in patient population, whether by age, duration of diabetes, initial HbA1c, cardiovascular risk profiles, or other factors somewhat obscures the generalizability of the data generated, even within large-scale CBD outcomes studies, and reduces the likelihood of demonstrating an effect for any given drug, particularly if

concomitant, anti-hypertensive, and lipid-lowering therapy are optimized in both arms of a comparative trial.

The second question is, does a specific therapy increase the risk of adverse cardiovascular endpoints independent of any improvement in microvascular endpoints that otherwise might lead to renal failure, neuropathy, or impaired vision? What is the risk-benefit ratio of a new drug as it relates to micro- or macrovascular disease or other potential, unusual adverse events?

These questions may best be answered by generating practice-based evidence on a large scale in diverse populations.

Clinical data currently suggests the treatment of diabetes patients should aim at obtaining a HbA1c between 6-1/2 and 7 percent, as suggested by the current clinical guidelines. Further reduction of CBD risk must be based upon multi-pharmacy

treatment of confounding risk factors. NovoNordisk believes that a routine requirement for pre-approval clinical studies aimed at providing hard endpoints, such as reduced incidence of CBD deaths or CBD disease, will create untenable delays in the process of diabetes drug development.

This may be particularly true for drugs that are targeted at the early stage of disease where the risk of cardiovascular events is low and the duration of follow-up would be long. This will make it virtually impossible to successfully develop new drugs directed at improving diabetes care.

On the other hand, if data demonstrating CBD risk marker reduction or obtained via RCTs, obviously preferably two independent clinical trials, we believe that certain labeling claims should be allowed. An example of these kinds of data would be blood pressure reduction during treatment if these changes are seen across multiple trials

in a clinical development program. We recognize the challenges of regulatory authorities differentiating between drugs in a given class of therapies based on different trial designs or different study populations.

Complexity and risks due to polypharmacy and heterogeneity, whether it be aspirin, statins, ACE inhibitors in different patient populations, as well as other confounders, will make class labeling appropriate and possible. If specific labeling should be granted, data must be solid and reproducible.

NovoNordisk applauds the FDA for taking the step to evaluate the current state of knowledge for diabetes biomarkers. We urge the Agency and the Advisory Panel to carefully consider the implications of requiring large-scale outcome studies prior to drug approval for drugs that do not have a signal of CV toxicity in pre-clinical and/or clinical testing.

Thank you for this opportunity to present the views of NovoNordisk on the current state of diabetes drug approval, particularly as it relates to cardiovascular disease. Working together to facilitate that timely approval of safe and efficacious drugs that can be turned into effective treatments for patients with diabetes is what this discussion is all about.

Thank you for your attention.

DR. BURMAN: Thank you very much.

Dr. Vigersky, who's president-elect of the Endocrine Society, is the next speaker.

COL. VIGERSKY: Good morning.

Mr. Chairman and members of the Advisory Committee, thank you for the opportunity to address the Committee today. My name is Robert Vigersky. I'm the director of the Diabetes Institute at the Walter Reed Health Care System, and professor of medicine at the Uniformed Services University of

Health Sciences.

However, I am here today as the president-elect of the Endocrine Society, the world's largest professional organization of endocrinologists, representing over 14,000 members. The Society would like to commend the Agency for its excellent analysis of the problem and its background introductory memorandum. In many respects, the issues raised in the memorandum encapsulate the conundrum of drug development in the 21st century.

How does our society encourage the development of safe and effective drugs by pharmaceutical companies without imposing draconian requirements that stymie these activities? Such inhibition would likely occur if the large, costly, and long-term studies required to assess clinical endpoints were required in the pre-marketing phase, before the FDA approval of diabetes drugs.

On the other hand, the FDA, our

patients, and their physicians should have as much information as possible in order to make an informed decision about whether or not the benefits outweigh the risks of taking any medication at any given point in time.

It is the timing of this available information on which we would like to focus.

Historically, pre-approval studies of diabetes drugs have been designed to show glycemic effectiveness because it is the sine qua non of approval. These studies have used HbA1c measurements for over 20 years as the surrogate endpoint because it most directly correlates with the microvascular clinical complications of retinopathy, nephropathy, and neuropathy.

While this relationship continues to be a well-accepted fact, what is not clear is whether there is a similar relationship of glycemic control to macrovascular disease and cardiovascular events, and/or whether or not these drugs -- there are drug effects that

are independent of glycemic control that influence the cardiovascular outcomes.

Since cardiovascular disease is the principal cause of hospitalization of patients with diabetes and cardiovascular mortality and morbidity, and it is the largest cost-driver in the care of patients with diabetes, these questions must be answered. But the pathway to do so is not obvious.

The Endocrine Society believes that a two-stage approach should be considered in the approval process for all new diabetes drugs. Studies initially should be designed and powered to capture both surrogate glycemic endpoints, such as A1c, and cardiovascular endpoints, such as lipids, CRP, and carotid intermedial thickness, as well as those adverse clinical endpoints, including all-cause mortality, fatal and non-fatal MI, and stroke, as well as beneficial clinical outcomes, such as delay

in the onset of renal failure, retinopathy, and neurologic damage. Having an appropriate control group for the entire study duration is essential to this approach.

A drug showing appropriate glycemic effects without an adverse short-term cardiovascular outcome could receive a conditional approval and labeling would reflect the interim nature of these results vis-a-vis clinical cardiovascular and other endpoints.

At some agreed-upon future time, the clinical macrovascular results would be evaluated and final approval granted with those results included in the new label. Improvement in macrovascular outcomes should not be a requirement for approval since the benefit of the drugs on microvascular disease would need to be balanced against the overall adverse effects.

However, worse macrovascular outcomes would be grounds to rescind approval

or substantially alter the label, such as having a black box warning. Because of the substantial additional expense that such studies would engender, additional years of market exclusivity for a drug might be a reasonable offset to the costs of doing these studies.

Finally, the Endocrine Society suggests that the FDA commission a study by an independent third party, such as the Institute of Medicine at the National Academy of Sciences, to evaluate and make recommendations about these critical issues that were raised in the background introductory memorandum and the subject of these deliberations, since these are pivotal for the future of drug development in the United States for diabetes drugs as well as other drugs.

Thank you again, Mr. Chairman, for the opportunity to address the panel.

DR. BURMAN: Thank you very much. The

next speaker is Dr. Zangeneh, representing, I believe, ACE.

DR. ZANGENEH: Good morning. Dr. Burman, members of the Committee, it's certainly a privilege to be here with you today. I've taken time from direct patient care to be here with you. As an endocrinologist who sees a number of patients with diabetes, I represent ACE, but the text of this presentation is all me. I speak for most, if not all, pharmaceutical companies that involve endocrinology and I consult with many of them. But I'm here today to speak with you with regards to diabetes and diabetes management.

I've been involved in many facets of diabetes from published research, contributions to diabetes guidelines, teaching, public awareness campaigns, and most important the care of people with diabetes. Churchill said success is going from failure to failure without losing your enthusiasm. So I think that's where we are

with CV trials with regards to diabetes: We need to carry on.

Diabetes is a multifaceted, multi-system progressive disease. Type 2 diabetes is an increasingly prevalent chronic disease that carries with it a formidable portfolio of associated metabolic derangements.

Treatment of diabetes should be individualized. There are over 24 million in the U.S. with diabetes, even in the pediatric age group, and diabetes is a global epidemic. Epidemics of diabetes and obesity will likely impact the GDP of many countries. There are population differences and polymorphisms with diabetes that even as an endocrinologist I can share with you that we still do not have a good handle about diabetes.

So if you still don't have a good handle about the multifaceted disease of diabetes, again, I think our clinical trials and our research is incomplete. But

certainly when the complete will come, the incomplete will go away.

We need to commence strategies for diabetes prevention. ACE has a diabetes prevention conference here this year in July, in Washington, D.C., to question the very premise that -- when does the risk begin? We don't even know. And of course, as you know, pre-diabetes precedes actual diabetes. And with that timeline not known, the incubation time of so-called the virus or the pre-diabetic or really diabetes is not known, how can we design good studies?

The impact of diabetes in the U.S., there are over 4,100 new cases a day, 810 deaths, 230 amputations, 120 kidney failures, and 55 new cases of blindness. Despite more than seven different classes of OADs, most people with diabetes do not meet ACE, IDF, or ADA diabetes guidelines. We still have unmet needs with regards to diabetes. We need multiple agents to address multiple defects

of diabetes. And as a clinician, most study agents fail very quickly and we'd run out of medications. And we also use insulin a lot in management of people with diabetes.

Duration of diabetes; baseline HbA1c; associated co-morbidities; adverse effects perceived, real, minor, major; data cell dysfunction; rapidly reduced suitable appropriate oral options for the patient; and because of these primary failures and loss of initial effectiveness as it was mentioned earlier, too often we have exhausted this large list of medications and we're actually running out of options for management of people with diabetes. And we use insulin early, late, and in the middle range with regards to diabetes.

Recent trials and studies have reminded us that diabetes and practice of management of diabetes is certainly a complex one. Recent trials -- ACCORD, VADT, and ADVANCE -- have been disappointing with

regards to CV outcomes, with regards to intensive reduction in HbA1c. Was it sub-clinical hypoglycemia, weight gain, excessive insulin, rapid A1c drop, or was it the lack of benefit? Was the lack of benefit due to inadequate length and design of these studies? I don't know.

In many way, this represents the view of -- old views that if you just fix the sugar, all other issues will go away. Just like the DCCT, UKPDS, Kumamoto, ACCORD, VADT, and ADVANCE. And we are not gluco-centric. We do approach diabetes in a multifaceted view.

Neither the advanced trial nor ACCORD undermines the importance of meeting or aiming the current guidelines for care. And this should not be interpreted as diminishing the importance of glycemic control. The lower than anticipated -- and this is very, very important -- the lower than anticipated the rate of CV events in the

intensive groups of these studies is an affirmation of the success of modern therapeutics, even when incompletely implemented. The advanced rates, my patients would actually enjoy those advanced rates because they were so low.

The results also underscore the difficulty of showing additional improvements in outcome since care is progressively optimized. Clinicians caring for people with diabetes should continue to focus on nutrition, weight reduction, smoking cessation, dietary and exercise counseling, blood pressure, aspirin, statins, and including A1C and blood sugar, but not limited to. We need more studies.

For now, rather than changing our guidelines or making early judgments, in order to better serve our patients we need to have more studies. While diabetes is a cardiovascular risk equivalent, the A1c real reduction remain uncoupled.

If we ask the wrong questions, we certainly will receive the wrong answers. We're asking a question that should diabetes drugs be evaluated for CV reduction? Is there a precedent? Do we do the same for statins and blood pressure-lowering medications? Do we do it? I don't think so.

I believe that the current design of studies are based on a previous array of knowledge that was based on our successful statin trials in the past. We were blessed as well as spoiled at the same time. Statin trials, most of which were stopped shy of their actual fruition time because of significant reduction in outcomes. Diabetes plays a different game. We're not waiting long enough. Short trials only detect adverse effects.

Lack of effect or background noise, meaning that indeed it is the disease that is doing the harm as opposed to the medications.

What is the definition of adequate

length of a diabetes trial? I argue that it should be longer than the sum of the duration of diabetes, which is not always known, and the pre-diabetes incubation time that is certainly unknown, but we're seeing the pediatric population becoming shorter and shorter. Trials that do not exceed the pre-diabetes and diabetes duration will likely not fit the bill.

The following questions are asked: The trials need to be long enough with adaptive designs that recognize the on-and-off targets. The glucose effect and the drug effect need to be outlined. And do we even have the right surrogate? Is A1c the right guy? Do we need PPG? Do we need a mean glucose? Research needs to go on. Duration of diabetes remains a variable, and that's very important.

So in the absence of evidence, meaning that absence of evidence is not evidence of absence, the strategies for

reducing microvascular complications is aggressive screening of diabetes, optimize glycemic control and blood pressure, but strategies for macrovascular are optimized by CV control, aggressive treatment of hypertension and other risk factors, management of diabetes, lipids, anti-platelet, weight reduction, and nutrition.

A greater effort than this needs to be necessary to broaden the focus on more cardiovascular complications of diabetes. Otherwise, we will be left with guidance mandating CHD trials and diabetes, none of which have been positive so far. But earmarking OADs with hard CV outcomes and endpoints would delay drug delivery. It would impact innovation and likely not improve the safety profiles of OADs.

As you know, it has been in post-marketing trials and studies. And when really the rubber meets the road, that many

issues have been -- risen with many things, including stents used for revascularization. We learn from actual experience.

This will lead to stagnation, a recession, and can impact modern American medicine.

We do, however, need strict and transparent post-marketing surveillance of new medications. And such an approach would complement the existing use of surrogate markets used to evaluate safety and efficacy of novel and approved drugs for management of chronic diseases, including but not limited to, diabetes.

Finally, when I come to my wish list for management of diabetes or an ideal agent -- because this was also brought up yesterday -- we searched for absence of hypoglycemia; easy administration; and medication that alters the natural history of disease, which is one of progression and beta-cell dysfunction; weight neutrality; a

medication that has reduced needs for monitoring, which is the most painful maneuver for a diabetic, the finger stick; efficacious and safety; and one the least micro- and macrovascular complications. We're not there yet, but we will definitely get there because such is the innovation of man, and I think we need more research.

But more so than that, we still don't understand diabetes in full. So I would definitely say here that we need more research and that when the good research comes, we will have better ideas about this.

Thank you.

DR. BURMAN: Thank you very much. And thank you to each of the speakers in the open public hearing. The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the

Committee as well as the public comments.

The first speaker to that end is Dr. Mary Parks, who will speak -- who has been -- asked permission to extend her time for a few minutes, for a few slides, to address some of the issues brought up yesterday, and certainly that was granted.

While Dr. Parks is getting ready, I want to remind everyone, the public observers at this meeting, while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel. And when Dr. Parks is ready, she will proceed.

DR. PARKS: Thank you, Dr. Burman. I'd like to first start off by acknowledging the guest speakers for their time, their participation, and their excellent presentations yesterday. I believe that they provided a very balanced perspective on a very important issue that we're here to discuss.

I'd also like to take this

opportunity to provide some clarification to issues or statements made yesterday. The first one pertains to muraglitazar. As many of you know, muraglitazar was not approved by the FDA, and this was after -- in spite of the favorable majority vote that muraglitazar should be approved at the Advisory Committee meeting on September 5th of 2005.

What some of you may not know is that when FDA does not take an approval action, our reviews are not available to the public. These reviews are not out there. It's most unfortunate, and I don't know if that will ever change or if there are any moves to change it. It's most unfortunate because what you don't see is the time, effort, careful consideration that FDA staff puts into these decisions that will ultimately result in the final decision.

And indeed, if you had the opportunity to see the reviews on muraglitazar, you would really see that the

FDA review staff on muraglitazar really should be acknowledged and recognized for their abilities to detect a cardiovascular safety signal.

And that, indeed, the credit really does go to the FDA review staff. I'd like to particularly note that Dr. Judy Golden -- unfortunately she's not here today; she was here yesterday -- was the primary reviewer who presented at the Advisory Committee that day, and she finalized her review four weeks after the Advisory Committee was convened with her concerns about cardiovascular safety and that additional studies were necessary. So again, my thanks to the FDA review staff for muraglitazar.

The second point that I wanted to make pertains to data presented for rosiglitazone.

Paul, do you mind pulling up the first one?

Yesterday, there was a slide that was presented regarding ischemic heart disease events that were taken from the rosiglitazone NDA. And these numbers were then used to calculate a relative risk of 1.8 with a confidence interval of .9 to 3.6.

That's not what is presented here. Some things I want to point out about that. Those numbers are based on ischemic heart disease events, and it's really unclear what "ischemic heart disease" events means. It can comprise chest pain, coronary insufficiency, myocardial infarction, angina, and I think what you're hearing here is that this is certainly one of the problems of these trials where they're not adjudicated.

However, in that same FDA review, one page after, there is another set of data presented, and this is actually for acute myocardial infarction. And what you see here, the ends are different for rosiglitazone because in this particular

table it is all patients exposed to rosiglitazone whereas the slide that was presented yesterday was only for rosiglitazone monotherapy patients. These are unique patients who had acute myocardial infarction.

And as in any clinical trial database, the control group -- or the investigated group is often studied longer than some of the control groups. They roll over into open-label extension periods. And so that also accounts for so many more patients exposed to rosiglitazone than the controls.

But here are the actual rates for unique patients and then corrected for patient new exposure. And I think really the point I want to make here is that this is not necessarily the best analysis to look at safety. I think that, Dr. Fleming, you may want to comment on, later on, the flaws of both type of analyses. But really what I

want to convey here is that the take-home message really should not be that there was conclusive evidence of a relative risk of 1.8 for myocardial infarction, myocardial ischemia, or even ischemic heart disease given the flaws in the previous analysis.

Okay. How do I move on? Okay. I believe I was tasked with some homework last night. And what I did was I looked at the NDA reviews for four anti-diabetic therapies. Not all of these drugs have been approved. And I have to say that given the short notice that I had to do this, I'm not entirely confident about the numbers.

I think they're very reasonable estimates. But for this reason, I'm not identifying the drugs, so -- but -- and for those drugs, these are all for first cycle reviews. Like I mentioned, some of these have not been approved.

And what you see here is total number of exposed to drug in an NDA database

range anywhere from about 3,200 to 4,300. Patient new exposure, anywhere from 1,300 up to as much as 2,600. And this column here, I am particularly less confident in these numbers here. The reason, as you heard, these are not adjudicated events. Although one particular NDA did have an adjudication committee for cardiovascular and cerebral vascular events. I was quite surprised when I went back and looked at that NDA.

But deaths, I'm confident about the number of deaths, although they may also vary depending on the cut-points for the database. Myocardial infarctions, where I did know that it was not fatal, I put that in there, but you may have some double-counting there. Fatal MI being counted, which would most likely also have been included. And then strokes.

We can put this slide back up again, but I wanted to at least provide that answer to the Advisory Committee panel.

I think that if you recall the slide yesterday, a proposal made with respect to -- I'm trying to pull up that slide, excuse me -- pre-approval cardiovascular studies, I think one thing that you can note here is that clearly patient new exposure as necessary will be much higher based on the proposal stated.

And the other thing here, I was not able to pull this up so easily, but the patient population risk, baseline risk for cardiovascular disease, the demographics, it's not -- because these trials are conducted both as monotherapy trials, placebo-controlled monotherapy trials. And as Dr. Joffe mentioned yesterday, you also have add-on trials. You have a spectrum of patient population with respect to baseline risk for heart disease.

Clearly, the placebo-controlled studies evaluating efficacy will more likely involve patients who are at lower risk for

heart disease because you really would have a difficult time enrolling these patients into placebo, even for a six-month period of time.

So these numbers here, if you take into consideration trying to apply it to a proposal where you want to enroll patients with even higher risk, I think you need to inflate these estimates even more than what was proposed yesterday. But again, we can present this slide later on during the discussion.

I'm going to now move on to what I had prepared to speak this morning. Okay. By this point, you've undoubtedly heard more and read more than I could possibly cover in 10 minutes on the regulatory history and drug approval process for anti-diabetic therapies and the long-term trials designed to evaluate the effects of these therapies.

Today's task is no easier for members of EMDAC and invited participants. You are indeed asked to take what you've

heard from yesterday's excellent presentations alongside your area of expertise and apply it in the discussions and ultimately on the questions on the role of cardiovascular risk assessment and approval of anti-diabetic therapies.

Now, before delving further into the discussion points and the questions, I think we need to take a bird's-eye view of what was presented yesterday. And what I have attempted to do in this slide here, I'm summarizing the timeline of availability of anti-diabetic therapies and also availability of clinical cardiovascular trials in patients with type 2 diabetes.

What you see first on this slide here is of historical interest to endocrinologists. This is the isolation for insulin from dog pancreas and over the next several decades how that had evolved into manufacturing animal-source insulins, and then the availability of recombinant

insulins, human insulins, and insulin analogs. And clearly over this period of time, this development, this really seminal discovery here in medicine, has markedly changed and improved the lives and well-being of patients with type 1 diabetes.

For the patient with type 2 diabetes whose disease is not marked by an absolute deficiency in insulin, yes, insulin is an option and it's a very effective option. However, if it were the only option, as it is today, we are talking about a daily injection, we're talking about risk of hypoglycemia and weight gain, and a lot of patients are reluctant to take that on. But fortunately, it is not the only option.

And in the 1940s, the first generation sulfonylureas were introduced; clearly effective at lowering blood sugars, but also associated with their own toxicities. And in the 1950s, phenformin, the biguanide phenformin was introduced; also

very effective at lowering blood glucose, but also associated with serious life-threatening lactic acidosis, which ultimately resulted in its removal from the market in the mid-'70s.

So if you focus only during the timeframe between 1920s and 1970s, those are the options for patient with type 2 diabetes: Insulin, first generation sulfonylureas, and phenformin. And it wasn't until the early part of 1970s, and you heard this yesterday, that the first prospective trial evaluating long-term benefit or long-term effect of glycemic control in type 2 diabetes was published.

And the results of the UGDP, again, as you heard yesterday, really, if anything, had more of a cautious tone than one of enthusiasm and endorsement of glycemic control for patients with type 2 diabetes.

Now, despite that, over the next 20 years, it really was not a quiescent period for drug development. As I mentioned

earlier, you have the different insulin products, the recombinant insulin products. You also have the introduction of the second generation sulfonylureas, which were very effective and carried less toxicity that the first generation sulfonylureas.

But perhaps it was with the publication in 1993 of the DCCT in patients with type 1 diabetes, and then in 1999, in type 2 diabetics, the UKPDS, that we now have definitive evidence, strong scientific evidence, that intensive glycemic control reduces microvascular complications in both these patient populations. And that information really enabled a broader acceptance of glycemic control as a primary measure of efficacy for the approval of treatments for type 2 diabetes.

And as such, in the last decade of the 20th century, you see available in the United States metformin. Actually, metformin was available in Europe before that time.

The alpha-glucosidase inhibitors, the thiazolidinediones, glinides. And then from 2000 to present, GOP-1 analogs, amylin analogs, DPP-IV inhibitors. And these are all therapies that do target different pathophysiologic processes in type 2 diabetes.

Stepping back from this timeline it should be apparent that the increase options and availability to patients really is a recent phenomenon.

I was struck by one of the presentations yesterday, Dr. Ratner's presentation actually. It was in two of his slides where he showed the incidence of end-stage renal disease in patients with type 2 diabetes, the trend of end-stage renal disease, and also visual impairment, the prevalence of visual impairment in patients with type 2 diabetes.

And perhaps if I was not tasked with homework last night, I could have

figured out how to superimpose his slide onto my slide here. But if you can just -- if you have an opportunity to look back at the slide, what I was struck was that the incidence of end-stage renal disease, it clearly showed that there was an increase. I think it started around 1980s, there had been an increase. But then it started to plateau, and it plateaued around this area. And I'm looking at Dr. Ratner, I want to make sure I'm not misquoting him.

And similarly, visual impairment in patient with type 2 diabetes, you start to see a slow decline in it. And the decline is starting to be much more noticeable around this area.

One would have to wonder -- and this is very good news. Yes, there's more that we can do for patients with type 2 diabetes, but this is good news. And one does have to wonder if by having therapies to control blood sugars and also to maintain

good glycemic control in patients who have failed their current therapies is, in some way, contributing to this.

Nonetheless, recent cardiovascular safety problems with some of the anti-diabetic therapies have raised the question of whether or not we need additional long-term studies with these therapies. And while we approve them for glycemic control, we do need to keep this in the back of our minds.

Interestingly, for all these therapies here that have been, as I say, more available as a recent phenomenon, have been studied in long-term trials, as you heard yesterday presented by several of the speakers. And I think that it's not unreasonable to say that if it weren't for the availability of these therapies, many of these trials could not have been conducted or could not be conducted at this point in time.

Trials that are looking at

intensive glycemic control versus standard glycemic control: Interestingly, if you look at the publication for ACCORD and ADVANCE, these are patients, a lot of them had to go onto two or three-drug therapy, a multiple-drug regimen. I believe 15 percent of the patients in the intensive arm for ACCORD required at least three drugs to achieve the degree of glycemic control that was intended for the intensive treated arm.

Trials trying to evaluate whether increasing insulin sensitivity or increasing insulin availability through an insulin secretagogue could also not be conducted. That's the BARI 2D trial I'm referring to here. If it weren't for the availability of these drugs here, it certainly could not have been done with therapies before 1990. So indeed, these drugs here not only were approved glycemic control, but have contributed to our current knowledge from long-term clinical trials.

However, in spite of a dozen of these trials, and I believe somebody yesterday mentioned that this is comprised of some 60,000 patients exposed anywhere from three to five years, we are still left with no evidence that conclusively established that one drug, any one drug, or any treatment regimen can reduce cardiovascular risk in type 2 diabetes.

And why is that? Was it the clinical trial design? Was it the patient population study?

Is it because this is a multi-factorial disease and controlling glycemia is unclear what role it plays or how much it contributes to cardiovascular risk reduction? Or is it the drugs that are being approved to treat type 2 diabetes?

It was clear from yesterday's presentation that treating hyperglycemia is important and it was also clear that nobody refuted its role in reducing microvascular

complications. But it's also clear that these are chronic use therapies and that many of the speakers and today, even this morning, at the open public hearing, that it is important that people are given enough information, physicians are given enough information with respect to risk and benefits to make informed decisions. These are, after all, chronic therapies and there are always concerns about off-target toxicities or unintended adverse events.

Now, a recent focus here is on cardiovascular risk with these drugs. And as such, this Advisory Committee has been convened to focus primarily on cardiovascular risk evaluation in the approval of anti-diabetic therapies. And so what I have here, I'm summarizing the only question that you are being asked to vote on. And I'm doing this to help you keep this in your line of focus through the course of the day. I anticipate there will be quite a bit of

debate and discussion, and at times it may veer off the question, important question, at the end of the day. And let me just summarize it again here.

It should be assumed that an anti-diabetic therapy with a concerning cardiovascular signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. Not only will that happen, but it has happened, as you heard with muraglitazar. And if you recall, there was a letter to the editor last year by several of us at FDA where we talked about a drug in Phase 2 that we did require that. In case anybody was wondering that was not muraglitazar. There was a lot of speculation. So we have done that.

And the question is, for those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial? And we're asking the committee to vote yes or no. If

you do vote yes, please elaborate and les us know the timing of such a study and when it should be conducted. Should it be conducted prior to approval or should it be conducted post-approval?

And though we did discuss this in our background package, and I know Dr. Joffe had also mentioned this in his presentation, there are no currently marketed anti-diabetic therapies with established evidence of macrovascular benefit. So please discuss, if you do vote that such long-term trials are required, how should that requirement be applied to existing diabetic therapies?

And with that, on behalf of the Division of Metabolism and Endocrine Products and the Food and Drug Administration, I'd like to thank you, the Advisory Committee members here. I look forward to your thoughtful deliberations and consideration and your final vote today.

Thank you.

DR. KONSTAM: Can we ask questions? Can I just ask a couple questions?

Thanks very much for your remarks. Just a point of clarification on the data that you showed about previous approval packages. So those were exposures to the drug, right?

DR. PARKS: That is correct.

DR. KONSTAM: So that wasn't -- you know, if you were envisioning sort of a program of controlled trials, the actual numbers that are sort of more pertinent to the question of how do you achieve a signal would actually be much higher than those numbers?

DR. PARKS: That is correct.

DR. KONSTAM: And the other thing, and similarly with the events, the numbers of events, those were just numbers of events in the active drug group; right?

DR. PARKS: That is correct. That table was all just active drug.

DR. KONSTAM: All right. So I'm just

sort of looking for the margin that might exist between what we might recommend and what you're presently doing. And I think it's narrower than it seems to be from that slide, the difference between them. I mean, I'm not sure we're as far away from where we need to go as I first thought when I looked at those numbers because of the total exposure in the -- including the control group patients.

DR. PARKS: Should we pull up that slide again just to make sure that we understand?

DR. KONSTAM: It might be worthwhile.

DR. PARKS: Because I'm not sure if I understand. Okay. So you're saying?

DR. KONSTAM: Well, I mean, the numbers we're going to -- I think looking at the proposal that was provided yesterday and some of Tom's comments and what we're going to be talking about today, we're really talking about -- you know, if we're talking about a trial, for example, total events in that trial

in both groups, this is just -- essentially would be equivalent in the right-hand column to the number of events just in the active drug group. So I just wanted to point that -- I guess I've got that right, that's all.

DR. PARKS: I guess the question here is that the slide yesterday, the proposal for pre-approval, is that total number of events for both control and study drug?

DR. KONSTAM: Right.

DR. PARKS: Or is it just study drug? And I'm not sure. I'm looking at that slide right now and I don't know.

DR. KONSTAM: Well, Tom might want to explain.

DR. FLEMING: Yes. So for example, in the two-stage approach that was discussed yesterday, where there'd first be a screening trial, if that screening trial had 125 events, then Marv is correct, you would expect about 60 in the active arm, 60 in the control. So 60 in the active arm would be the number to compare to

those numbers.

And if it were a 2-1/2-year follow-up study in the 2 percent per year population, it would take about 1,250 people probably 2-1/2 years, is about 3,000 people, 3,000 treated people, 3,000 person -- 1,250 people followed 2-1/2 years would be 3,000 person years on the active arm. So you're right, Marv, the numbers aren't extraordinarily different, maybe on the order of doubling, tripling what is currently there.

DR. KONSTAM: Can I get one other point of clarification on what Dr. Parks said? So the question as you rephrased or restated the question to us today, I just -- a point of clarification, you referred to "a" cardiovascular trial. And so another option might be a program of trials in which there was a standard, common adjudication process and a standard, common accounting of cardiovascular events across a program. So that in essence one

could view it as a sort of trial equivalent among a series of trials. I guess I just want to -- when you -- I mean, were you going to ask us to vote should there be "a" cardiovascular trial? I guess I wonder whether the question's not slightly broader than that.

DR. BURMAN: Well, Dr. Parks, do you want to respond, or Dr. Temple?

DR. PARKS: I think that the way the question is worded is specific, "a long-term cardiovascular trial," which is a single trial designed to assess cardiovascular risk. Now, what's not stated in there, but this is why -- and this was intentional because, as you know, in the items in Discussion 1 and 2, we're asking you to also deliberate on whether or not this trial should be designed to demonstrate benefit or to rule out a particular risk, an acceptable increase in risk. And so that's what the intent of that is.

Now, Item 1 in your discussion also talks about how we can improve the current

safety review or safety database. And we do talk -- let me see if I have the questions before me, but I believe one of the items discussed is meta-analysis of safety trials. And I'm not sure that's what you mean there by multiple trials designed in such a way that --

DR. KONSTAM: Yes. I mean, somebody on the panel might feel very strongly that we've got to do a lot better at cardiovascular safety. But there may be another way of doing it other than saying there must be a large cardiovascular trial. I guess that's sort of the nuance that I'm asking about.

DR. BURMAN: Marv, we're going to be -- when we're done with this session, we're going to take a break. We have other questions now, but we're going to take a break and then we're going to reconvene and we're going to go through each of the issues, not just the discussion. So we'll have ample opportunity to discuss each of those issues. And we do want

everybody's view on those and we'll be going around the table asking everybody's views.

But Dr. Temple, you had another comment as well?

DR. TEMPLE: Well, I had a question about numbers. The proposal that Dr. Nissen made talked about getting better information before you go on and do the large trial, presumably by looking at pooled data and -- nobody's even talked about it -- presumably that actually could be a mixture of active control and placebo control and all that.

The presumption that that would take a much larger database than we now get, however, seems to me to depend on which way the data are leaning. If, for example, you had 20 to 38 or whatever it is number of events, and the number was the same in both groups, that might well be sufficient all by itself with that database to rule out the upper limit of two. The upper limit of two gets harder to rule out when it's leaning

adversely, as those numbers from yesterday show. So it really sort of depends, that might not be a much larger database than we now see based on those. It really all depends on how the data are coming out. And I just wanted to see if Tom thinks I understood that right.

DR. FLEMING: It's certainly true that what the point estimate would be or how the actual balance in the data would be has great influence on what you can rule out. And so the numbers that are shown here are based on what size trial would you need in order to have a high probability of being able to rule out what's unacceptable? If, in fact, the data are highly favorable -- if, in fact, let's say you're truly benefiting this endpoint and your estimates are highly favorable, you can rule out an unacceptable margin with a smaller number.

The number two, though, needs to be viewed with great caution because obviously we have to discuss what is the upper limit of

what would be an acceptable level of increased risk.

DR. TEMPLE: Right. But whether it's 2 or 1.8, the numbers here are what it takes to rule out If the point estimate is 1.31 or 1.26 or something like that -- if the point estimate is 1, that is if it doesn't look like it's leaning adverse, then you need a considerably smaller number of events and a considerably smaller number of total population; right? Or, I mean, I just want to be sure I'm not missing that.

DR. FLEMING: So if you look at the line with 122, the second line from the bottom, that's the number that you would need in order to have a high probability of being able to rule out what would be an unacceptable rate. And essentially, the bar for what would be the least favorable result you could accept would be a 26 percent increase.

DR. TEMPLE: Right.

DR. FLEMING: And so if you were

saying I want to have only a 2-1/2 percent chance of saying things are okay when you have an 80 percent excess, and a 90 percent chance of saying things are fine if there's no excess, then that would take 122. But as you say, Bob, if when the first 60 events come in there are 40 in the control and 20 in the intervention, so you're having the event rate, clearly you can then, at that point, rule out not only an 80 percent increase, but maybe even a 20 percent increase or 30 percent increase.

DR. TEMPLE: Right, but those numbers are to dream about.

DR. FLEMING: Correct.

DR. TEMPLE: Suppose it was just 30 and 30.

DR. FLEMING: Correct.

DR. TEMPLE: So that the estimate is not 1.26, but 1, then you wouldn't need numbers like are shown up there to rule out 1.8. It would be considerably smaller; right?

MR. PROSCHAN: No, you would need

those numbers. That third column is the limit of what would be acceptable. So if you get 1.31, like in that second row, then you would pass the criteria. You still are using the number of events that's on the left side. It's just that that third column tells you how big the hazard ratio estimate could be and you'd still accept the upper limit of the confidence interval is less than 2.0, for example.

DR. TEMPLE: Yes, I understand that. But suppose the hazard ratio crudely -- well, small numbers -- wasn't 1.31, but was 1. It just came out even. Then you don't need numbers like that to rule out 2.

MR. PROSCHAN: Right.

DR. TEMPLE: So if it were 1.8 or whatever it is.

DR. FLEMING: If it were 1, then you could rule out a 67 percent increase. If it were 1. Now, obviously that's not adjusting for any kind of multiple (inaudible) that you're doing and all of that.

DR. TEMPLE: That's right. But those big numbers come if you're leaning adversely.

MR. PROSCHAN: No, no.

DR. TEMPLE: No? Why not?

MR. PROSCHAN: Those numbers on the left are what you would need in that first trial, that screening trial. Those are the numbers that you would need. And so that result of 1.31 is for that screening trial in which you had that number of events.

DR. TEMPLE: No, the 1.31 is described there as the point estimate.

MR. PROSCHAN: That's right.

DR. TEMPLE: So the point estimate is what you observed.

MR. PROSCHAN: Right.

DR. TEMPLE: Suppose you didn't observe a risk of 1.31, but observed a hazard ratio of 1?

MR. PROSCHAN: In that screening trial with 87 events.

DR. TEMPLE: Yes. Well, whatever the

number events. My contention is, if I understand you, you'd need many fewer events if the hazard ratio was 1 to rule out the upper limit of two. You wouldn't need as many. That's the sort of worst case. That's the largest point estimate you could rule out -- that's the largest point estimate you could have and still rule out an upper limit of two.

MR. PROSCHAN: In that screening trial, which has 87 events.

DR. TEMPLE: But that's because it came out badly distributed from the drug company's point of view. There were more events in the treated group than in the placebo group.

MR. PROSCHAN: Right.

DR. TEMPLE: But it doesn't have to come out that way.

MR. PROSCHAN: Right. No, I'm -- but what I'm saying is that has implications for what you then require in the second trial if, indeed, you even require a second trial.

DR. TEMPLE: Well, that's true.

MR. PROSCHAN: So this first trial does require that number of events. But then, depending on the results of that first trial, you could say, okay, now I don't need a second trial. For example, if you ruled out a 10 percent increase or if you ruled out any increase, then you'd say I wouldn't need this second trial. But -- so what you're saying has implications for the size of the second trial, if there is one. It doesn't have implications for the size of the screening trial.

DR. TEMPLE: I don't understand that. Show the next slide, could you? Can you do that? No, the one with the figure. Yes.

If it was coming out like No. 3, you have way more events than you needed to rule out 2. You didn't have to have 35 and 52. You could have done with half that.

MR. PROSCHAN: But are you saying you would look at an interim point in the screening trial? Because you still -- this is the

screening trial that you're seeing.

DR. TEMPLE: It's not a trial, I mean, if I understand. Steve can talk for himself, but I understood that this would be a look at the cumulated data in the Phase 2/3 studies. It's not a trial. So we need to go into how you look at it periodically and what adjustments you'd make, that's more complicated than we want to get into. But you don't need anything like 35 and 52 if it's leaning favorably. You could get away with way less and still rule out the upper limit of 2 or 1.8 or whatever it is you wanted to rule; right?

DR. BURMAN: Yes, I understand what you're saying. I agree with you and we'll talk about this some more.

DR. TEMPLE: Okay.

DR. BURMAN: And we certainly want to thrash this out. If I may, Dr. Nissen, you had a comment as well?

SPEAKER: A point of clarification.

DR. BURMAN: Yes.

DR. NISSEN: Bob, I understand exactly what you're saying. The challenge here is that with adjudication of events, there's this considerable lag phase and so on, and you're not going to really know what the point estimate is until you're very, very late in the game. And so this becomes then a matter of a strategy.

And if you were to start a development program that had fewer events than that, I mean, I don't think it would be wise for a sponsor to do that nor would it be wise for the agency to encourage that. Because you could get all the way through the development program with fewer than those number of mandated events and then you find out what your point estimate is.

And so the reason I proposed this is I think that guidance to industry to say, look, these are the number of events we think you need during this development program in order to reassure us that you've got a drug that's not going to have a high level of risk

for adverse cardiovascular outcomes.

Now, I didn't define how this was to be done. But as I'm sure Tom will discuss, if you do this by pooling of multiple trials, there are some significant downsides compared to doing this in a single, well-designed, properly adjudicated pre-approval study.

And I did not -- I deliberately didn't answer that question. I mean, I think that's a great question to ask this panel today, is could you get there by doing a bunch of smaller studies and accumulate the number of events that you would need, or does this need to be a single well-performed, carefully adjudicated study?

And I will leave that discussion to the committee. I have my own opinion about that, but I do think that you can't know when you start the development program what your point estimate's going to be. And I don't think anybody would want to take that risk

when you set that upper limit of 1.8 or 1.5 or whatever.

DR. TEMPLE: They might want to take the risk. That's what we were talking about. They might even say, heck, if the point estimate is 1.4, I'm forgetting about this anyway. I don't want that drug. That's too risky for me to make it available because I'll probably have to yank it later.

DR. NISSEN: Yes.

DR. TEMPLE: So there's a lot of decisions one could make.

DR. NISSEN: Yes, there are, but I guess -- I think some rigor here is needed because I can -- since we do these kinds of trials all the time, I can tell you, you get all the way through it all and then you're going to find out what your point estimate is, and it may be 1.1, it may be 1.0, it may be .9, but you're not going to know that when you started.

DR. TEMPLE: Yes, but recognize although it's maybe not exactly what you're

talking about, a sponsor submitting an application carries out an integrated analysis of the safety data. Believe me, if the -- after correcting for exposure, if the deaths or something bad looked much worse, we don't not see that; you do see that. And as Mary said, on some occasions those hints have made us ask for large studies.

So something to discuss is whether you can do this cumulatively, whether you can collect data as you're going along. Those are very good questions.

But if it's leaning favorably, I mean, look at the top example, the .98. You don't need 4,000 people to know that.

DR. BURMAN: Dr. Temple, I agree.

DR. TEMPLE: Okay.

DR. BURMAN: We'll -- and very good points and we're going to discuss those. And as I say, I think I understand the issue.

Before we break and then have further discussion, I wanted to ask Dr. Parks

if I really understood these right. If you could put up the previous slide of Dr. Nissen on this one for a second. It had the patient -- yes, that one.

Dr. Parks, am I understanding this right? I'm just trying to get an idea of how many patients we would have to increase the number of trials with if we were going to alter the present regulatory advice. And that is, on this slide, just taking the events for one example of a point estimate of 1.31. With a 2 percent annual rate, you'd need 4,350 patient years. And the slide you showed today, if I wrote it down correctly, of Drugs A through D, you said that they had 1,300 to 2,600 patient years. So that's really in the same ballpark of what we're asking -- may ask in the future compared to what we're doing now.

DR. PARKS: One thing I mentioned up there is that this also needs to take into account the baseline risk of these patients and

whether or not you're going to be able to accrue the expected event rate that was in the previous slide. These are numbers from the current development program. And although they are patients who are going to be with established heart disease, they're not going to be -- I really doubt, I seriously doubt that they will be at such risk that you're going to be able to get that kind of event rate in the current development program. So I don't know how much it would be inflated, but I do believe it will be inflated if you need to enroll patients at a greater risk to be able to achieve that kind of event rate.

DR. BURMAN: Thank you. Any other questions? Please.

DR. FRADKIN: In terms of the question of how much increase in number of patient years would be required from what's currently done to what's proposed, I think the point that Dr. Nissen just raised as to whether this would be an amalgam of studies versus a single study

is absolutely critical. Because, I mean, sponsors are going to want to be able to get their drug approved as monotherapy and as add-ons to the most commonly prescribed drugs. So if what we needed was -- you know, many of the studies that go into what Dr. Parks presented was the combination of studies for each of those indications. So if you needed that plus a single study to address the cardiovascular versus an amalgam, it's going to make a huge difference in terms of what the magnitude of the increased number of patients is. Maybe --

DR. BURMAN: Thank you. And it also depends obviously whether you require that pre- or post-approval.

Dr. Goldfine?

DR. GOLDFINE: And again, I also just want to stress that in order to achieve these kinds of events rates in the Nissen model, one actually would need to be looking at the highest risk individuals.

And we're now taking new drugs and exposing, again, the highest-risk individuals, who may have the least ability to survive from an event. Therefore, the mortality or absolutely hard outcome to these individuals may be greater than if we pick up signals from our healthier individuals who may be able to cope with these events. So it is a balance and tradeoff when you're investigating, especially in a brand-new class of agents.

DR. BURMAN: Dr. Rosen?

DR. ROSEN: I don't know if we have to do it now, but it would be helpful for the FDA to re-specify to this group what the development program currently is so that we can contrast that with what is proposed in respect to a single trial versus a development program, which includes multiple trials and other aspects.

DR. BURMAN: Dr. Joffe, I think you mentioned some of that yesterday. Would you like to respond to that?

DR. JOFFE: I'd be happy to. Would it be useful to see some of those slides again or would you like me just to speak without the slides?

DR. BURMAN: If you'd like, with your slides, please do.

DR. JOFFE: Are those easily accessible?

DR. ROSEN: I think it's just a little confusing for some of us when people refer to a "development program" to understand exactly what that refers to since it's clear that there are some studies involved in that. But we'd like to know whether there's pooling of data, how the data's pooled, and how that would contrast with another proposal.

DR. JOFFE: So this is a typical Phase 2 program, which usually has 1 or 2 -- we prefer 2 -- dose-finding trials, typically 12 weeks in duration, patients who are either treatment naive or on a single anti-diabetic drug, are randomized to one of multiple doses of

an investigation or agent or placebo. Typically in one of these studies there's anywhere between about 40 or 50 patients per treatment arm. So in terms of size for this type of Phase 2 clinical trial, you're talking maybe a couple hundred patients, 300 patients or so. And there may be 2 of these, so you're looking at 600 patients. Again, this is only over 12 weeks. Some of these doses are not going to be carried into Phase 3.

With regard to the Phase 3 program, these usually consist of let's say five or six six-month randomized, double-blind, control trials, and then several extension trials. Or the patients from these individual trails might feed into a single extension trial. And these five or six core six-month randomized, double-blind, control trials are conducted in several scenarios. Usually there's one or two monotherapy trials. Monotherapy could either be placebo-controlled. Occasionally we see a

non- inferiority against an active control such as a sulfonylurea or metformin.

And then there are four or so add-on combination trials. So these are add-ons to other commonly used anti-diabetic drugs. These are usually add-on to a single agent. As I mentioned, I'll come back to these in a little while.

As I mentioned yesterday, the core program, it'll be an add-on to a metformin trial and an add-on to a sulfonylurea trial, and add-on to a thiazolidinedione trial. And then there's usually a mixture of whatever else a company would like to do, whether it's an active-controlled, six-month monotherapy trial; add-on to other agents such as the newer approved agents, such as a DPP-IV inhibitor; add-on to insulin; or add-on to dual agents or sometimes even triple agents.

And these are, as I mentioned before, six-month trials, typically testing one or two doses of the investigational agent

versus either placebo or the active comparator. These studies are usually powered on efficacy, but because we've told sponsors that they need to have these minimum sample sizes of 1,300 or 1,500 patients at one year, they often bolster the numbers in these trials to make sure that they have enough safety for those sizes.

DR. ROSEN: Is that 13- to 1,500 total for the studies?

DR. JOFFE: Thirteen- to 1,500 exposed to -- treat investigational drug. What we've generally been using as guidelines -- and this is just very general; it really depends on the drug you see -- but we tell folks that we'd like to see roughly -- a minimum of 200 patients exposed to investigational drug for at least one year in these different combinations. So as an add-on to metformin, we'd like to see at least 200 patients exposed to one year; add-on to sulfonylurea, at least 200; add-on to TZD, at least 200.

Are there any other specific questions on the Phase 2/3 development program?

DR. BURMAN: Thank you, Dr. Joffe.

Dr. Rosen, does that answer your question?

DR. ROSEN: Yes, extremely helpful.

DR. JOFFE: While I'm here, I might just add one thing, which I would like the committee to comment on, and that's this issue of how diabetes progresses over time and how we can get long-term control trials. This is really going to pertain to the -- if you think we need a clinical -- a cardiovascular trial. Because as I mentioned before, we can't leave patients on placebo for a very long time and diabetes progresses. And so additional therapies get added. And then the question is how do you tease apart the effects of the drug you're trying to test.

DR. JENKINS: Hylton, while you're there, you also have a slide of the sample size

for the safety analysis. You might want to show that as well. I think you went past it.

DR. JOFFE: I wasn't sure, is it this slide or the --

DR. JENKINS: No, the ICH slide versus what you're asking for in the safety database. Someone smarter than I might be able to quickly calculate how many patient years of exposure that bottom of the slide would result in. You're asking for 300 to 500 exposed for 18 months, so someone can do that math. You've got 13- to 1,500 for a year and the, of course, it gets more difficult for the 2,500 Phase 2/Phase 3 total. But if you argue those are about three- to six-month trials, you could ballpark what the patient years of exposure -- and these are for drug exposure, not the total database.

This is drug exposure; right?

DR. JOFFE: Correct, correct.

DR. JENKINS: So that could tell you what your program would result in as far as

patient years of exposure relative to some of the slides you've seen earlier.

DR. ROSEN: Quick question. Mary mentioned the number of trials that were adjudicated during this development program. Was it just one that you said that had complete CV adjudication?

DR. PARKS: I only -- again, this is at 3:30 in the morning, looking at these NDAs. Some of them were 450 pages long. But I did see in one particular NDA reviewed that there was a CCV committee, adjudication committee, and there was also an Internal Medicine Committee. But for the other ones, I seriously doubt that there was an adjudication. It's not common to have an Adjudication Committee for Phase 1, 2, and 3 trials.

DR. BURMAN: Thank you. Dr. Rosenbraugh, did you have something? No? Okay.

Dr. Temple?

DR. TEMPLE: I just want to make the

observation that we expect companies to monitor their total programs as they're ongoing. It would be inexcusable if a company wasn't looking at total mortality as the trial was going on and things like that. So part of what has to be thrown into this is the fact that there has to be some degree of monitoring as the trials are accumulated.

DR. BURMAN: All right. Any other questions for the FDA, Dr. Parks?

Then I think it's appropriate and we'll take a break a few minutes earlier. Please remember that there should be no discussion of the meeting topic during the break among yourselves or any other member of the audience.

I've got about 9:30. Should we resume at 10 to 10:00?

(Recess)

DR. BURMAN: Why don't we get started for the panel discussion? The plans are for the next two hours or so until noon, when we break

for lunch, to discuss the points for discussion and the questions to the Advisory Committee.

And what I'd like to do is to read the introductory paragraph so everybody is on the same page. And then with regard to each of the questions -- and we don't have to vote on any of the questions except No. 3 -- but when -- we would like a full and thorough and detailed discussion from every member of the panel regarding each of the issues.

So we'll be going around in order and asking people their opinion. And I think that's very valuable for the FDA to get the summary opinion. And at the end of each question, I'll summarize as best I can sort of a consensus statement.

To get started, as a brief background that we already know, all drugs that are currently approved by the FDA for the treatment of diabetes mellitus are indicated to improve glycemic control. The FDA and many leading medical organizations