so we averaged the four years together, and you see with acute myocardial infarction the different ranges there, with biguanides on the bottom, insulin on top and Avandia and actos in the middle between the two. Also, with CHF you see the same with the Avandia and the actos fairly close together between biguanides and insulin.

The bottom line is that we did not see any increased incidence in select cardiovascular events in these two categories among our beneficiaries who filled a prescription for Avandia compared to those who filled prescriptions for other anti-diabetic medications.

There are several limitations to this way of looking at the data and looking at claims data, so we were not able to determine from this data if the difference in the average annual incidence rates of the outcomes were due to an anti-diabetic drug itself, to disease progression, number, types and severity of comorbidities or other risk factors such as age. We also had a limitation in this population because when they turn 65 they become

Medicare eligible and, therefore, we are no longer the primary insurance for them; we are secondary. Then, the claims data did not include any socioeconomic status, comorbid conditions, current health status, their medical history, duration of drugs, time on the drug, any other medications that they were taking, and any other characteristics like body mass index.

Also, a couple of other limitations to this way of looking at the data that we found when we looked was that the cause-effect relationship saying that the MI or the CHF outcome would be directed back to the medication that they were on, so there is obviously some concern there. And, because the drug categories were not mutually exclusive and that we had patients on multiple medications, as the rest of the population in the nation would, we were unable to make any statistical comparisons for significance in this area.

So, as we go forward, we basically find that our big net was not able to see any outlier,

but we might need to make the net tighter. Therefore, we propose either looking at retrospective cohort study and to dig into the medical--

DR. ROSEN: Thank you very much. Speaker number nine?

DR. NUSSBAUM: Good afternoon. My name is Sam Nussbaum. I am wellpoint's executive vice president and chief medical officer. I have no financial relationships with any pharmaceutical companies.

WellPoint is the nation's largest health benefits company, providing medical coverage for more than 34 million Americans. In addition to our 14 Blue Cross and Blue Shield plans, we are the parent to a number of subsidiary companies, including HealthCore, which is a health outcomes research company. Because WellPoint also has subsidiary companies that perform disease and care management and provide pharmacy benefits, we are able to have comprehensive integrated medical and drug information for our members.

We have provided copies of this presentation to the committees and a more detailed analysis of the study is available to you. HealthCore has conducted an analysis to provide additional insight into the safety of the TZDs compared to other oral anti-diabetic agents. I am pleased to present these findings to you.

Specifically, over the past five weeks our safety and epidemiology and health plan analytics team have examined five years of integrated claims data, from January 1st, 2001 to December 31st, 2006, for five of our WellPoint health plans to determine if there is evidence in the real-world setting of an elevated risk of myocardial infarction in patients receiving rosiglitazone or pioglitazone. This study was funded entirely by WellPoint.

As I will outline in the subsequent slides, HealthCore found no evidence of an increase in risk for either acute MI or unstable angina in patients taking these drugs. The study was a retrospective, longitudinal cohort design using integrated pharmacy, medical and member eligibility

data. We determined acute myocardial infarction by review of all medical claims for care in the hospital and in the emergency room using ICD-9 code. In addition, to enhance the sensitivity analysis we expanded the definition to include unstable angina to look at all acute myocardial events.

All patients who were taking insulin or actually taking both TZDs during the evaluation period were excluded. Importantly, the severity of illness and the complications and intensity of diabetes was determined by evaluation of covariates, including marked risk for cardiovascular risk in the year prior to initiating therapy.

We performed a multivariate Cox proportional hazards model to evaluate the independent effects of exposure to the two TZDs and other oral anti-diabetic agents on the risk of acute MI. Baseline cardiovascular risk factors were adjusted for a cardiovascular risk score.

To assess the impact of the definition of

outcomes and exposures, we conducted extensive sensitivity analyses and, finally, we looked at the risk of acute MI to determine if there was a difference in patients taking any of the available oral anti-diabetic agents as monotherapies.

The cohort included 22,000 patients treated with rosiglitazone and almost 24,000 patients treated with pioglitazone, and 120,000 patients treated with other oral anti-diabetic medications. What is important, again, is that patients taking both TZDs had different baseline characteristics. Most notably, patients in the TZD cohorts were older by 3 years and had a higher Dale Carlson score, indicating greater comorbidities. In addition, a higher proportion were men.

Patients using rosiglitazone had higher burden of cardiovascular risk factors, such as prior MI, a composite ischemic risk index or stroke events compared to all other patients taking other oral anti-diabetic medications. In addition, patients in the rosiglitazone cohort had higher use of cardiovascular disease-related medications that

may have impacted the risk of acute MI, for example ACE inhibitors, beta-blockers, nitrates, platelet aggregators and lipid-lowering drugs were all used in a greater percentage of the TZD-treated patients.

HealthCore's researchers also evaluated the occurrence of the hospitalizations due to diabetes in the presence of diabetic complications across the three cohorts. Again, the TZD patients had almost twice the hospitalizations, greater burden of complications, including nephropathy and retinopathy, as patients treated with oral anti-diabetic agents. Again, this was prior to treatment.

Regarding cardiac events, we observed 212 acute MIs in the rosiglitazone-treated patients, 232 in the pioglitazone-treated patients and 866 MIs in the patients taking other oral agents, for an incidence rate of 0.73, 0.74 and 0.72 heart attacks for each 100 patient-years of therapy. When we included angina, the events became even more manifest, 415 in the rosiglitazone group, 414

in the pioglitazone group and 1613 events in the oral anti-diabetic group, with incidence rates of 143, 133 and 133.

The hazard rate for acute myocardial infarction associated with patients taking rosiglitazone was 1.029 as compared to other oral anti-diabetic agents, and the hazard rate for pioglitazone was 1.044, neither statistically significant. For all acute events, again, no statistical significance. When we limited our analysis solely to those on drug treatment period, again, we had a hazard rate of 0.945 for rosiglitazone and 0.90 for pioglitazone, not statistically different. We evaluated subgroups of patients that were taking monotherapy, almost 6,000 Avandia, 9,000 actos, and again no statistical difference.

This study is unique in several experimental models that we will share with the committee in the presentation. In conclusion, we found that patients taking either Avandia or actos did not have a higher incidence and prevalence of

acute myocardial events. Thank you.

DR. ROSEN: Thank you, Dr. Nussbaum. Welcome.

MR. RALSTON: Thank you. I am Richard Ralston, executive director of Americans for Free Choice in Medicine. My organization received a contribution of $50 from an employee at Pfizer a few years ago, which was later matched with a gift of $50 from Pfizer. No other gift from a pharmaceutical firm or organization has been received, nor any reimbursement for travel expenses. We are a non-profit organization, providing public education on free market approaches to healthcare. We advocate the principles of individual rights to physicians and patients and personal choices as the only proper basis for healthcare policy. We support the economic and moral rights of businesses to make profits as a result of developing and producing medications, and their investors to obtain a substantial return on their investments. We hold that this provides the best hope for the

development of new drugs for America and the world.

I should also say that I have been managing my own type 2 diabetes for some years. I have previously taken Avandia but now rely on insulin after participating in a clinical trial of Atlantis a few years ago. I have no qualifications to evaluate the safety or efficacy of any prescription drug. I am not a physician or a scientist. I do not know how to conduct a clinical trial or how to evaluate the results of such a trial. I do not know how to evaluate a meta-analysis of multiple clinical trials.

I have been told that it is possible to compile the apples of one clinical trial, conducted under one set of criteria and controls, with the oranges of another clinical trial, conducted under another set of criteria, but exclude the grapefruits of yet another clinical trial because it reported no adverse events, and then somehow to come to a conclusion not reached by any of those that actually conducted the clinical trials. I have to say I don't understand it or even know

whether it has more study power than clinical trials.

In other words, my limited understanding of these methodologies puts me at approximately the same level of competence as the chairman and members of the House Committee on Oversight and Government Reform. But I was not born yesterday. When results of a meta-analysis claim that a drug is killing people and should be taken from the market, why is it first reviewed with the majority staff of the committee of the House of Representatives as a part of discussing, quote, pending legislation, unquote? On what basis did the chairman of that committee instantaneously issue a press release evaluating the findings of the meta-analysis and describe it as, quote, a case study of the need for reform of the nation's drug safety laws, unquote?

Was this based on the chairman's vast clinical experience or on his mature understanding of the human endocrine system? If not, was his press release itself a case study, but a case study

of how to distort, manipulate and manufacture research data to support a political agenda?

If patients taking the drug are presumably dropping in the streets of heart failure, why is a prestigious medical journal first take the time to write an editorial in pursuit of a political agenda as a part of publishing the research?

Lastly, why would someone who has been publishing clinical research make the statement on a national television program, broadcast to the general public, that, quote, the deaths caused by Avandia could dwarf the carnage of September 11, 2001, unquote?

As I am not familiar with the austere technical terminology of reports of clinical trials, could someone explain to me what were the exact clinical results and what were the precise metrics to justify such a statement? And from the perspective of objective peer review, what could have been the purpose of such a statement? Is there something else going on here besides science?

I am concerned that the tremendous power

of the Food and Drug Administration over the health and daily lives of Americans has become a magnet for those with another agenda. To mention only two, there are those with so much antipathy for private business as such that they would rather see people suffer and die for want of new medications than allow anyone, anywhere, to make money from developing them. There are some law firms already hovering over Avandia as a contingency fee jackpot of billions of dollars who would prefer to see any drug driven off the market, no matter how many people it helps, if it presents an opportunity for a litigation bonanza that will only result in higher drug prices.

My chief concern is what happens to patients in this process. What happens when patients are frightened away from drugs that are helping them, or when physicians are intimidated from prescribing approved drugs? Do politicians using press releases or researchers making polemical statements on television care about what they are doing to the countless patients that have

been helped by a drug without adverse effects?

There are two distinct issues here which I would like to call to your attention. First is the politicization of research. Secondly, and more importantly, is what the use of such tactics implies about the core skills of the researchers and the reliability of their conclusions. Why are such tactics necessary if the science speaks for itself? When should publishing research be turned into a political and public relations campaign in the general media? And why? And to researchers who behave in this way employ the same tactics with the same zeal against drug companies that fund their research against those that don't?

I am sure that I do not need to tell this committee about the importance of relying on objective information and not on things they hear on ABC's "Nightline." Those who manipulate research for the purpose of increasing the powers of the FDA, which they can then further manipulate to achieve their political objectives, must not be allowed to control this process. Please rest

assured that many of us realize all of these factors and what you have to contend with to make your decisions. Thank you.

DR. ROSEN: Thank you very much. Speaker number 11, please.

DR. DAVIDSON: Dr. Rosen and members of the panel, I am Janie Davidson. I am an endocrinologist that sees patients almost every day. I am with UT Southwestern and I used to be sitting on that side a few years ago. It is easier to be on this side.

DR. ROSEN: Thank you.

DR. DAVIDSON: And having been on the other side, I will tell you that I am here to actually congratulate the agency and all the presenters today for excellent presentations. I am here on my own. Even though I am an advisor to several pharmaceutical companies, nobody invited me; nobody paid me; nobody invited me for breakfast and I didn't eat lunch. There was no place where to eat.

Then, you know, if we look at the issues, we wouldn't be doing so well controlling diabetes

in the U.S. We would not need new drugs. I think David Nathan is right. We would not see diabetes as the leading cause of blindness, as the leading cause of amputations, as the leading cause of renal disease, and Dr. Ratner suggested that. You know, he showed the data. I am not going to present that. But also, with duration of diabetes and age, you know, congestive heart failure is a big problem and there is no question that, you know, coronary artery disease is the killer of patients with diabetes.

I am here because I see patients and I am here, and I work with the agency because all of us believe that we don't want to do any harm. There is enough being done to patients with diabetes. But, you know, when we look at editorials that are one-sided, you know, and for us in the practice of diabetes, in general practice, we don't know where to go because we don't know what to do with the information because it is one-sided, you know. And, we give the media a field day for bashing. You saw today bashing here, in the FDA. And, that

is not, you know, a civilized world. We are here to work together and if we all work together we are going to see better diabetes in the future.

I do not know, because we have the excellent panel of people, you know, what the end result will be but I have some questions, more than I have answers really. But, remember, bashing should not be part of our culture. Okay? I know, because I work for the agency as an advisor, that the agency is always open to anybody that wants to talk to them and I urge you to do that.

You heard as well that control is not optimal in the U.S. It may be a little bit better, but in Texas we still have a lot of problems. I heard today that the A1c is not any longer, you know, the gold standard as far as diabetes is concerned because in the studies that were shown today A1c did not correlate with the risk for cardiovascular events. But I want to know if the A1c was part of the analysis, if A1c in the studies was considered as an endpoint, you know, not because the drug was given, everybody was with an

A1c at 7. And every single trial. UKPDS showed that the A1c decreases cardiovascular events to some degree, but mainly microvascular events and those are very important.

The next question is over time for patients with diabetes, we don't know if in the studies we looked at the duration of diabetes. You know, duration of diabetes is very important. Obviously, in the background the question was asked what lipid-lowering agents were used, and it is not only statins. Remember, statins only lower the risk by 30 percent in patients with diabetes. But if we can have some data not only on statins but other drugs to lower lipids, it would be very helpful.

Well, I hope, you know, that today you will reach at least the right decision. You know, we need help in patients with diabetes in the United States. If we would be doing well I would not be here, and I tell you coming back is a learning experience. Thank you very much for all your help.

DR. ROSEN: Thank you very much.

MR. STEELE: Good afternoon. My name is Charlie Steele. I live in New York City and I was diagnosed with type 2 diabetes in 1987. Like many diabetics, I have suffered the consequences of diabetes--heart disease which resulted in two bypass operations and peripheral vascular disease resulting in a left below the knee amputation, not to mention the big toe on my right foot.

I am here today, speaking on my own initiative and was not requested to speak by GSK. My words are my own and I did not share them with GSK. I did request some help with the travel expense but I am not on any GSK drug. I am on different diabetic drugs.

I know a little more about diabetes than the average diabetic because I keep myself informed almost on a daily basis about diabetes because in my volunteer work I deal a lot with diabetics, particularly diabetics with limb loss. I am on the board of the Amputee Coalition of America, headquartered in Knoxville, Tennessee, and I am a

member of their medical advisory committee. I focus on diabetes and limb loss in most of my volunteer work.

Vascular complications from diabetes is a primary cause of amputations in this country. On average, 225 people a day lose their leg because of diabetes. Unfortunately, 70 percent of that could be avoided. But, again, I am here on my own initiative. I am 61 years old and lately my hemoglobin A1c numbers have been creeping up. My doctor tells me that my system is just not as efficient as it used to be since I have had diabetes now for 20 years even with the lifestyle changes I made where I exercise three or four times a week two hours a day. I understand that this is not unusual. The longer you have diabetes, the more that your system is going to change and not process your glucose even with your medications.

I have been on one oral diabetes drug for over 17 years and I personally believe it is losing its effectiveness with me and my system. As a patient, like someone mentioned earlier, I want as

many effective medications and options in my doctor's arsenal as possible. From what I read and hear, and even today with all the coverage on this issue, I have been sensing a lot of hype and overreaction, and it concerns me greatly. I am reading conflicting reports and studies on health websites like Medline plus news, and all this is enough to make one's head spin.

I just want this committee to come to a thoughtful, rational, fair and educated conclusion, and with this epidemic we need all the weapons to fight this disease that we can, and it is my understanding that Avandia has been an effective medication for over eight years for up to three million diabetics. But the biggest thing that pushed me to testify today at this hearing was the fact that my 84-year old mother was diagnosed with diabetes last year and she has a history of not tolerating prescription drugs and medications. She tried two or three diabetes medications with her doctor but experienced side effects. When she was prescribed Avandia she had no side effects. Since

May, when this became a massive news item, she hasn't taken any medications at all for her diabetes. That worries me. I would rather see her on a medication with close monitoring for a specific possible side effect than no medication at all. And, if another medication works better for me as my body changes, I would opt for closer monitoring as well rather than risk more consequences from this nasty disease. That is what risk management is all about, and I understand that is the title in part of this committee.

In conclusion, I am asking you to please let good science and common sense influence your decision and not any outside pressure. Whether at the end of the day your consensus is to leave it as it is, recommend new label warnings, pull the drug, or whatever, will be fine with me as long as it is a fair process. And, believe me, someone talked about we all have skin in the game, diabetics have the most skin in this game. Please think about the patients. Thank you.

DR. ROSEN: Thank you, Mr. Steele for a

lovely presentation. I hope you keep your volunteer work going. Congratulations on a nice presentation.

DR. TOLBERT: I am Jerome Tolbert, an endocrinologist from New York City. I feel like I am perfectly placed; number 13 is a great spot.

First, I want to thank the committee for allowing me to participate in this discussion in this hearing regarding Avandia. I do participate in a number of speakers bureaus, the BMI being one Pfizer Pharmaceuticals, Santa Fe Aventis and GSK. They did not provide any financial support for transportation however. I am here on my own and have no other disclosures.

In my opinion, because of the growing diabetes epidemic, Avandia is a medication we need to help fight this disease. We need drugs of all classes to fight this disease. Avandia is not a perfect drug, but it is a drug that I feel is extremely useful and effective.

One of my patients came into the office just recently requesting that he be taken off

Avandia. The reason he wanted to be taken off Avandia is because his family was upset after looking at the news media. He was very comfortable with the drug himself. But after a long discussion I decided that I would, in fact, take him off of Avandia.

Now, this is the hitch, I have heard or stories where doctors have discontinued Avandia without giving them any type of follow-up, just stop taking the medication, not go to your primary care doctor, go here, go there, get medication, make sure you control this disease, just stop the medication. I think this is a real problem for us because it is, in fact, happening and I think it is going to contribute to this worsening diabetes problem that we have.

As an endocrinologist practicing in New York City, I have specialized in diabetes for over 20 years, and during this time I have witnessed an explosion of this diabetes epidemic which concerns me greatly, especially as it relates to African American and other minority groups, such as

Latinos, Asians and Native Americans. These individuals suffer disproportionately from this disease. I have worked closely with many organizations involved in diabetes care, and I can tell you those who are intimately involved with taking care of patients and care about diabetes feel very passionately about it. We understand the difficulty in controlling this disease and trying to prevent these complications.

Over the years I have witnessed an explosion of knowledge about diabetes. It has been fantastic, everything that we have learned, more about pathophysiology, more about its complications. And, I have also seen the development of new medications. In 1997 a new class was introduced to us called the TZDs. It took me a long time to learn how to pronounce thiazolidinedione but I got it down now. But this is the only class of oral diabetes medications that truly targets insulin resistance, which is the one of the core defects, if not the core defect in diabetes. It is the only class.

I have treated many patients successfully with Avandia and feel very comfortable with this medication. Avandia has allowed me to gain control of many of my patients when I otherwise would not have done so. Here is an example. This was a longshoreman, obese, who needed insulin to control his diabetes. He was so afraid of using a needle, and I pride myself on being able to get people on insulin but he was so afraid that he absolutely would not go on insulin. Consequently, he was placed on three oral agents, one being Avandia. Guess what, this patient has been under control over five years with Avandia and two other oral agents. It really shocked me to find that but I was very, very pleased.

There are side effects with all medications but we learn to recognize these side effects and to make adjustments when necessary. Avandia has been a great help to me in treating my diabetic patients. We know that about two-thirds of the American population are poorly controlled in terms of their A1c. They don't even get down to an

A1c of 7. We know that many will develop severe diabetes complications. Many will die and die prematurely. With this poor glycemic control, we will continue to see increasing cases of kidney failure, blindness, amputations and other complications, particularly in minority populations.

I am here to express my concern that Avandia may not be available to me for my patients in the future. I am concerned that severe restrictions of its use will further contribute to this worsening diabetes epidemic. Again, there is no perfect drug for treating diabetes. We know, however, that using these drugs in combination allows us to gain control of many of our patients. I need Avandia and all the diabetic drugs in my armamentarium to help me fight this disease, this deadly disease. My goal is to help improve the lives of all my patients with diabetes. I thank you.

DR. ROSEN: Thank you very much.

DR. TOLBERT: Dr. Trippe wasn't able to get

here and he asked me if I would read his.

DR. ROSEN: You have a minute credit.

DR. TOLBERT: I just got this. Thank God, it was typed. Doctors don't write too well. Dr. Trippe states that he could not be here because of weather conditions and he could not get a flight out, but he is one of the key opinion leaders in America. He is also on the speakers bureau of Eli Lilly, Aventis, Merck and all pump companies, Pfizer and GSK speakers bureaus. He has no stock or other disclosures to reveal.

I want to thank the committee for allowing him to give this testimony. He does say though that I don't envy the board's dilemma of making or revising rosiglitazone's role in the positioning of treatment of type 2 diabetes.

Please commiserate with a very hard working clinician, teacher and endocrinologist whose primary goal is the prevention and scientifically safe approach to this epidemic. However, we define type 2 diabetes, we all understand that it is not jut glucose toxicity. I

have tried since 1995, as a board-certified endocrinologist and a founder of the American Association of Clinical Endocrinologists in Alabama, to alter and ameliorate diabetes. Without insulin sensitizers, my job would have been even more difficult, especially coming from the Black Belt and epicenter of, quote, central obesity in central Alabama.

What my colleagues and I are trying to do is save the beta-cell. As this epidemic exploded, I and my patients have dreamt of ways to prevent type 2 diabetes and about therapies that are both safe and efficacious. Applying them to the largest solo practice of diabetes in the United States, I am the leading pump provider as well as the number one provider of inhaled insulin. These distinctions, however, are not what I am proud of. What I am excited about is the possible, probable prevention of type 2 diabetes. So far, so good with execution, aggressive use of USC in combination with secretagogues and sensitizers such as Avandamet, my large, quote, obese practice

experience has not found what the current ideological and statistical crisis has found. In fact, just the opposite. Truly it is a conundrum that a drug so ideologically protective has statistically been shown not to be.

I am a practicing endocrinologist, not a statistician, but my gut tells me, based on all PPAR-gamma agonist benefits clinical trials since 1999, that rosiglitazone is protective, not problematic. And, he has used these drugs in over 2,000 patients whose BMI has been over 30.

I and my clinical colleagues are puzzled. Why should the science differ from the experience? As we torture the data, our patients are tortured by this schismBmeta-analysis versus the real world; vascular disaster versus endothelial inflammation protection. The practicing diabetologist applauds rosiglitazone. In my practice of more than 30 years there has been a decline in ischemic vascular events, not an increase. This is using live patients, not dead numbers. The recent *New England Journal* data and the editorials make no biological

sense.

These issues remind me of when I was a young endocrinologist, the oral sulfonylureas that are still out there, are still just as toxic as years ago. It also reminds me of teaching fellows and residents about glucose control and A1c's. It is not how low you go, it is how you go low. Rosiglitazone fits that bill. My patients are living proof.

As the panel knows, our country is struggling to keep the insulin resistance syndrome in check. So far, the glitazones have helped, not hurt. If the TZD tools are no longer available in our therapeutic toolbox, as patients and caregivers are now terrorized by the media and legal scavengers, let's remind ourselves that new onset type 2 diabetes is truly an oxymoron and rosiglitazone has prevented more diabetes disasters than any statistician.

It sounds like Bruce! Do we treat with non-clinical data or trust ourselves? In God we trust. All others have to show the data. Our

problem today for the FDA is who do you trust? This is from Dr. Bruce Trippe. Thank you.

DR. ROSEN: Thank you. Speaker 15?

DR. TURNER: Thank you very much indeed. I am here of my own volition as a clinical research scientist and methodologist and a patient advocate. Despite my English accent, I am an American citizen and it is a privilege to address you all today. I will talk fast with an English accent.

My university has paid my travel and my hotel expenses. I have recently authored two pharmaceutical-related books for John Wiley and Sons, and co-authored an introductory statistics textbook for Pharmaceutical Press. I will receive royalties. I offer medical writing services and educational seminars to the pharmaceutical and CRO industries. I have done work for Health Decisions and GSK in this capacity. I was a GSK employee for two years, until November, 2005, when I joined the faculty at Campbell University. My wife is a current GSK employee. My wife and I do not own any individual stock in any company. We have exposure

to the pharmaceutical industry and many other industries in large capital retirement mutual funds.

Two recent events have caused too much attention to the topic of today's meeting, publication of a meta-analysis in the *New England Journal* and a political committee meeting on June 6 that generated nationwide media coverage of this paper. As the Chairman of the Department of Clinical Research, I am deeply concerned by both events.

At that June meeting, the limitations of the meta-analysis were not given the emphasis they require by the authors or consequently by the media. Consequently, a very large number of patients have unnecessarily been caused considerable psychological anguish and Lord only knows how many of these have suffered transient myocardial ischemia or worse as a result of that stress. Whichever Latin pronunciation you prefer, this does not appear to be first do no harm.

Mr. Chairman, you said some of us might

get passionate. Very respectfully, in this morning's meeting I felt as though we were in a methodological twilight zone. Specifically, the comment that the evidence presented is not enough to refute the meta-analysis seem extraordinarily strange to me. This means, in effect, that we have set up the results of the meta-analysis, with its myriad of limitations, as a quasi null hypothesis, and the experimental data from RECORD do not allow us to reject this null hypothesis is taken as evidence that the meta-analysis is, indeed, correct. Maybe I missed something in epidemiology 101, but this is just not right.

The *New England Journal* article is like a rubber mallet that is being given the weight of a sledge hammer. But, please, don't take my word for that. Let me quote from the paper in question. Since I am the last speaker, it seems maybe appropriate to bring it around to full circle. I quote, a meta-analysis is always considered less convincing than a large prospective trial, designed to assess the outcome of interest. Although such a

dedicated trial has not been completed for rosiglitazone, the ongoing RECORD trial may provide useful insights, end of quote. I believe we heard such insights this morning from Dr. Stewart.

So, what actions are appropriate? I respectfully would like to suggest a couple. I only have two quotes and, again, I will read them. You don't need to hurt your necks. In their report on the future of drug safety, published in 2007, announced in September, 2006, the Institute of Medicine noted that the role of the regulator is not to impede the development of innovative medicines but to ensure that needed drugs are available to patients and that risk/benefit information is accurate and widely available. In addition to the excellent work of the drug safety committee, the risk communications advisory committee, their work may well be extremely beneficial in providing information to patients.

The second quote is from the FDA's own risk management document. The risk minimization action plans guidance states that FDA views the

management-Bsorry, I apologize, this is from the risk map guidance. FDA views risk management as an iterative process encompassing the assessment of risk and benefits, the minimization of risks and the maximization of benefits. This guidance also says, and I quote, FDA recommends that risk maps be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients. The foundation of a successful practice of medicine is the medical knowledge and clinical judgment of the physician and his or her knowledge and relationship with the individual patient. The most beneficial avenue in pharmaceutical medicine is to serve patients by providing accurate information and guidance to physicians, and then allowing these physicians to discuss this information with their patients and to prescribe medicines they deem best for each patient on a case by case basis. This avenue allows them to provide the greatest therapeutic benefit to the majority of patients and the greatest degree of

protection where needed.

I implore you, trust your individual medical colleagues around the country. Trust them to do the right thing. Give them the information they need and then allow them to work with individual patients as a health team, a medical doctor and a patient, and let them work together for the patient's benefit. Thank you.

DR. ROSEN: Thank you very much. The last speaker?

DR. ZANGENEH: Z always goes last. Thank you so much. My name is Farhad Zangeneh. I am an endocrinologist from northern Virginia. I serve on speakers bureau of many pharmaceutical companies with regards to diabetes or metabolic disease, including GSK and Takeda, the makers of TZDs. I also serve on the board of directors of American Association of Clinical Endocrinologists. I am an assistant clinical professor at George Washington.

I am here on behalf of my patients. I am speaking as an individual. I also want to thank my patients for allowing my staff to reschedule them

for this afternoon so I can be here for my presentation. So, I thank everyone for that.

I have received no financial assistance to be here today for travel or for food, or for any item of that sort. I have been involved in many facets of diabetes, from published research, contributions to diabetes guidelines, teaching, public awareness campaigns and, most important, I take care of people with diabetes.

I am not a mathematician. I found that out today. I am a clinician. I am an endocrinologist and I think that is where the rubber meets the road. As you know, type 2 diabetes is a chronic, prevalent disorder. It is a progressive disease that carries with it a formidable portfolio of associated metabolic derangements. There are over 21 million people in the U.S., even in the pediatric age group, with diabetes, a number that continues to grow. Cardiovascular disease remains the single most common cause of death in people with diabetes. Two out of three people with diabetes suffer a serious

diabetes-related complication, and management of diabetes generally requires multiple classes of drugs that work in complementary mechanisms to address every defect of diabetes, which is a multifaceted disorder.

Despite advances in our therapeutic armamentarium, *Findings from the State of Diabetes in America*, issued by AACE, revealed that two out of three people are not reaching the recommended AACE guidelines of 6.5 percent or less. Reduction in hemoglobin A1c has been shown to reduce micro- as well as macrovascular complications, and there is also accumulating evidence that improvements in glycemia are important predictors of better diabetes outcome. Recently as part of a diabetes awareness campaign, I had the privilege of meeting Ron Spring, retired former Dallas Cowboys running back who told me, he said, in my playing days I was tackled by Michael Singletary of the Bears, Lawrence Taylor of the Giants, and he said, my friend, nothing has hit me as hard as diabetes. I am an amputee and I have also had renal

transplantation. So, this is why you are here today, and I am sure you will do the right thing.

As with all therapy, there are multiple potential adverse effects and physicians must appropriately guide patients to optimize therapeutic guidelines. I do know that the ADOPT and DREAM studies are landmark clinical trials indicating durability of diabetes control and delaying development of type 2 diabetes with rosiglitazone respectively, both of which are promising news for people with diabetes. TZDs improve insulin sensitivity, improve beta-cell function, lower blood pressure, improve hypercoagulability, dyslipidemia, inflammation, parameters of non-alcoholic fatty liver disease and reduce carotid intima-media thickness in people with diabetes. The improvements in these surrogate markers have made them attractive choices for use in management of people with diabetes.

Patients read newspapers and advertisements and surf the Internet. They take part in clinical trials and raise money for

research. They have the greatest stake of all of us in the outcomes or research. Patients seek more effective safe treatments and better management of diabetes to include improved quality and quantity of life.

Since the May 21 release of the meta-analysis in the *New England Journal of Medicine*, 75 percent of physicians surveyed in one industry report say that they have seen non-compliance, decreased compliance or abandonment of their medications with regards to diabetes. Every day in my practice we receive patient phone calls regarding concerns with ongoing news surrounding the TZDs. These issues need to be addressed and we need help. My staff asked me, they said to me that this is like the national security. Every day there is a different color coding with the use of TZDs. So, this needs to stop.

I do know that meta-analyses have substantial limitations and this requires specific discussion that exceeds my allotted seven minutes.

I do want to refer you to an elegant written testimony by my colleague, Dr. Zachary Bloom garden. As we heard today in the studies mentioned earlier, ADOPT and DREAM, there appears to be no increase in significant risk of ischemia with regards to rosiglitazone. The data safety monitoring boards of the BARI 2D and ACCORD have met and reported new increased risk among people receiving rosiglitazone in these trials, recommending that these studies should proceed unchanged. I do know that, as with most medications, TZDs have side effects. I also know that absence of side effects does not translate into safe. I do know that treatment inertia does not carry zero risk, and on a daily basis clinicians weigh the risks and benefits of any therapy for our patients.

The last thing people with diabetes, people that are in the battles dealing with this chronic disease need to be concerned about is the confidence in the medications and the recommendations set forth by the clinicians. This

resembles a soldier that in the midst of battle in trenches has to question the integrity of his armor and the accuracy of his guns.

I do, however, advocate a renewed way to review and disseminate way in a dispassionate, de-politicized way and free of sensationalism. I do know that good science will clarify the conclusions. I do know that science is a constant variable. I do know that patients demand good science and only with proper assessment of data, and only with good science we can answer these questions. I do know that we will likely not have much clarity until BARI 2D, ACCORD and RECORD have been completed. I am also for strict and transparent postmarketing surveillance of new medications, and such an approach would complement the existing use of surrogate markers used to evaluate safety and efficacy of novel drugs approved for management of chronic disease.

The medical community, including myself, needs a clear, concise message to give to our patients, and I would hope that FDA delivers a

position that would clarify the current state of ambiguity with the use of TZDs in the care of people with diabetes. I thank you and good luck.

DR. ROSEN: Thank you very much. This concludes the open public hearing. We are going to move immediately to the committee's discussion, without a break. I just want to set up some guidelines and some discussion points.

Two critical things that I need to mention, Steve Nissen and Curt Furberg are here prominently so that we can ask questions as a committee, if there are any questions concerning analysis, meta-analysis and the outcome studies the way they have written them. So, I would suggest that that might be a possibility if there are questions in reviewers' minds about the analysis or the debate.

We have five questions that have been posed to us. Two require a vote. When we get to the vote I will explain the procedure for the vote, which has changed somewhat. But the three questions are all sort of interrelated and they

relate to your concerns or feelings about the meta-analysis, the randomized trials and the observational trials.

My feeling as chair is that we should first spend about 20 minutes or so in a discussion period that is open and free for anybody on the committee that wants to start the discussion about what has been heard. Particularly, we had no time to really talk about the FDA discussion we had earlier, and I am sure that some of the committee members would like to address some questions about that.

After the discussion period, which can go much longer than 20 minutes, I will individually poll people around the room in order and ask them their feelings about the three different types of studies, what their strengths and weaknesses are in their perspective. Then we will move to a vote. So, I would like to start the discussion by just opening up questions and I am going to start on the left-hand side because I have a blind spot on my left side; I have been told so. We will start with

Dr. Geller and Dr. Goldfine. Either of you can begin the discussion.

Questions to the FDA/Discussion

DR. MOSS: Will the people who are on telephone conference be included?

DR. ROSEN: I am sorry, Dr. Moss and Dr. Oakes, yes, you will be included. I have notes about you but I got a specific request that I needed to acknowledge people that were left leaning.

DR. GELLER: Thank you. I have a question for Miss Mele, which is related to the fact that you conducted a very comprehensive, detailed analysis. It is quite clear you were very thorough. I wonder though if you considered a random effects model which is another method for meta-analysis. That was one of my questions.

The second to you is what about all those analyses? Did you consider any corrections for the multiple analysis?

MS. MELE: I did a lot of analyses and one of the analyses I did do was I did do a random

effects model for risk differences, and I did that for all the meta-groups and also for the overall estimates. So, I did do that.

DR. GELLER: Were the results the same?

MS. MELE: They were really very consistent. And your second question was?

DR. GELLER: Was about multiplicity, the many, many analyses you performed and whetherB-

MS. MELE: Well, we didn't consider multiplicity because this is a safety issue. If it was efficacy, yes, we would have considered it but we didn't because it was safety.

DR. GELLER: Actually, I have the same question for Dr. Nissen. Did you conduct the random effects meta-analysis, and were the results consistent?

DR. ROSEN: Dr. Furberg, you will go right after Dr. Nissen.

DR. NISSEN: We did and we got essentially identical results. We actually put it in a letter to the editor of the *New England Journal*, which will be out in a few weeks, just in response to

other letters. Did you have a second question?

DR. GELLER: Well, I have the records of somebody else's meta-analysis on your data using the random effects model which, because the zeroes were included, pulls the estimates closer to 1 and nothing becomes statistically significant.

DR. NISSEN: Yes. We didn't see that. In fact, we got virtually identical results using both models, and you will see that analysis.

DR. GELLER: Did you include the trials with zero events?

DR. NISSEN: We did.

DR. ROSEN: Dr. Furberg?

DR. FURBERG: I had a question for the FDA, not in answer to you. Are you all set?

DR. GELLER: I have a question for Dr. Graham as well.

DR. ROSEN: Okay.

DR. GELLER: You showed a lot of comparisons of rosi and pio, putting them on the same slide.

DR. ROSEN: He is not here so maybe we will

come back to Dr. Graham. Dr. Furberg?

DR. FURBERG: Well, we have seen a lot of slides today and I think the most informative in my view is the one that Dr. Joy Mele showed, number 17. Why do I say that? Well, she took all the 42 trials and divided them into the placebo-controlled and the active-controlled trials. And, we have to remember that these trials address different questions. The placebo-controlled trials answer the question does rosiglitazone increase the risk of cardiovascular events. I think the answer is clear. There is an excess risk, statistically significant. The active-control trials answer a different question. It asks how does rosiglitazone compare to others.

In my view, I think it is totally inappropriate to pool those data. It doesn't make any sense, and I want to pose that question to Bob O'Neill. Bob, do you think it is fair to pool the placebo-controlled trials and active-controlled trials and come up with something that is almost impossible to interpret?

DR. O'NEILL: Well, I think there is a reason why Joy Mele presented that slide. A lot of time was spent thinking this through. To a certain extent, I think David Graham's presentation addressed those--

DR. FURBERG: He did it as well, yes.

DR. O'NEILL: Yes. So, I think you are exactly right, they are asking different questions because they are using different comparator groups, but they are also fundamentally asking different questions. So, the short answer to your question is that the reason the whole pooled analysis sort of gives you almost the same result is because 85 percent of the data is the placebo-controlled data anyway. So, the sample size is just driving that overall result in the point estimate. It is not really terribly sensitive.

There is another issue here relative to Dr. Geller's point, and I would like maybe the committee to sort of grapple with this because there is not a whole lot of precedent for how one thinks about the level of, quote, statistical

significance that should be attached to an exploratory finding, even if it is, quote, a safety issue. And, for a meta-analysis that, you know, at the end of the day comes up with a p value of 0.0453 it might be argued that it is not that impressive from a statistical significance perspective.

The nominal part of this is sort of dealing with the many different comparisons that could have or should have been done. Let's say we had ten studies in the beginning and somebody wants to pile on another five, and another five, and another ten, and when do you end? So, the issue of how do you sort of come to grips with how much is enough and how much is enough relative to the exploration part of it, we don't have answers to this. But this is a long-winded response. Joy Mele thought long and hard about presenting this just so you could feel the way you did and why you asked the question.

DR. FURBERG: When I look at the table by adding the active controlled trials, I dilute the

clear finding from the placebo-controlled trials. I think it is a mistake to combine them. It is misleading.

DR. ROSEN: Dr. Graham is back, if you want to address that question.

DR. GELLER: In many of your slides you compared rosiglitazone to pioglitazone, and if you think about it, the highest level of evidence is head-to-head comparison in a randomized trial, of which you had GLAI which comprised 735 patients and exactly 9 cardiac adverse events. I think the evidence for that comparison is pretty minimal. Comments?

DR. GRAHAM: Yes. Part of the problem is that these drugs have been on the market for seven and a half to eight years and there have been no large head-to-head studies. So, what I was in a position of looking for was whatever evidence there was. That happened to be all the evidence there is so I presented it. That, in conjunction with other evidence and sort of how many different compass needles and in which direction do they point in,

and what is the consistency across the responses is a point of view I was trying to convey to the committee.

Another point that I was trying to convey as well is that the standard of definitive evidence, which in a sense is what underlies your question, is something that statisticians talk about all the time and wanting p values that give them a very high level of certainty about the correctness of the decision. We are in a situation where we don't have definitive events but the question is what is more than likely happening, what is happening to patients and what is happening to a large number of them? You may not share that view, but that is the perspective that I am coming at it from. And, when I look at the totality of the evidence, what I see is repeated consistency of where the bulk of your confidence interval and your point estimates point to an increase in coronary heart disease risk, and I don't see any offer of evidence of major clinical benefit with rosiglitazone.

For five or six months internally that was one of my repeated refrains, and what comes back is there are no unique advantages. So, the question then is if there is a reasonable chance that you are causing harm with this drug and you don't have any evidence that you are gaining benefits and there is another drug that is exactly like it, as best as we can tell in most of the features which we are able to measure, which is pioglitazone, then why would you want to give rosiglitazone to anyone? I have just explained to you my reasoning.

DR. ROSEN: You are okay?

DR. GELLER: I am okay.

DR. ROSEN: Dr. Holmboe?

DR. HOLMBOE: I just want to go back first to the comment about the p values. I worry we are spending way too much time talking about p values. The only thing a p value tells you is about the statistical stability of the results and I hope, you know, that we take into account the clinical significance of what we are talking about here.

I mean, if you actually calculate the

numbers needed to harm, which is a far more meaningful sort of statistic in trying to figure out the safety of a drug than a p value, you know, I found today that I can get a number needed to harm anywhere from around 70 up to 3,000 so I think that it just shows you it depends on how you crunch this data.

It goes back to an article from the *Annals of Internal Medicine* from 1991 that said did you ever meet an analysis you didn't like? I think that we have to be very careful that we are over-extrapolating from multiple analyses. So, I just want to make that point that we ought to be focusing on whether we think this is safe.

My take on most of the conversation today is that the safest drug is placebo for diabetes. You know, that seems to be the safest drug. Take placebo and you are going to be a lot better off.

One other point, Dr. Graham earlier referenced an article from *Annals of Internal Medicine* which will be out in September that I didn't think he fully represented, and that was

from Bolon, et al., talking about the comparative effect of the various drugs. I want to point out from table 1, which I have up in front of me, when they looked at all-cause mortality, cardiovascular disease mortality, cardiovascular morbidity, peripheral vascular disease and microvascular outcome, they could not find any conclusive evidence for any oral diabetic agent with regard to one being more effective than the other. In fact, the level of evidence that they rated for all those comparisons was low to very low. And, I think it is important that this committee be aware of that.

DR. ROSEN: Thank you. I would like to go to the telephone people and then I will go around the room. Arthur first.

DR. MOSS: Yes, thank you. It seems that the emphasis has to be on drawing conclusions based on good science, and we heard about the standard of clinical evidence. So, the central question is does rosiglitazone increase cardiovascular events or increase cardiovascular risks? We heard all about all the limitations of p values, power and

meta-analysis.

You have to remember that diabetes is a chronic disease with recurrent cardiovascular events, and everything that we heard from all the analyses looks at the hazard ratio for the first cardiovascular event, not for multiple cardiovascular events. That is, has any of the statisticians associated with the FDA or with GlaxoSmithKline carried out an analysis with multiple events as the outcome? That is, using an Anderson dual model, particularly with regard to the individual studies? Because that would dramatically increase power and significance level, and would allow possibly a definitive conclusion. Because we are not really interested in just what is the first event unless, of course, it is death, but multiple events. One can handle the death issue in such analyses. So, I would be interested from the statistical people with the FDA if they at any time looked at an analysis related to multiple events.

DR. ROSEN: Any comment from the FDA? Dr.

Mele is making her way here.

MS. MELE: We actually initially talked about this. The database was not set up like that. It was all first event type outcomes. But we did discuss it. I discussed it with both of the clinicians, Dr. Gelperin and Dr. Mahoney, and we decided that because it is only six-month data and the event rates are so low that it was not a worthwhile thing to do, to look at the recurrent events.

DR. MOSS: But is that just focusing on the six months? What about the longer-term trials?

MS. MELE: Well, we have only briefly reviewed ADOPT. We don't have DREAM and we don't have RECORD. So.

DR. ROSEN: Arthur, hang on a second. Dr. Krall is going to make a comment from GSK.

DR. KRALL: Very briefly, the long-term trials primarily captured only the first cardiac event. There are, to our knowledge, very few second events.

DR. ROSEN: Thank you.

DR. MOSS: That is unfortunate because diabetes is such a chronic disease with recurrent MI, recurrent angina and bypass surgery. You have heard from all the patients and, yet, that is not being included as an endpoint where you would have the power to begin to see whether rosiglitazone increases cardiovascular risk and cardiovascular events.

DR. ROSEN: Tom Pickering?

DR. PICKERING: I have a question for the FDA, I guess Dr. Mele, about the evaluation of events. Your assessment of what was an event, is that the same as the applicant's assessment? Also, in many of your analyses in your strongest case was for the combination of serious and non-serious ischemic events, and I am not clear how they were categorized. For example, if you had a patient who was admitted with chest pain and dyspnea who might be a case of heart failure, would that be counted as a non-serious ischemic event?

MS. MELE: I don't know the answer to the second question but I can answer the first

question. You wanted to know why we analyzed serious and non-serious events and whether it was the same as GSK's. Right? We used the GSK database and our clinicians reviewed the events in that database. So, we are analyzing the same events that they are analyzing.

DR. PICKERING: Was your scoring the same as the GSK events?

MS. MEYER: I just wanted to clarify, there is a regulatory definition for the word "serious" and you mentioned specifically being admitted to the hospital. That does meet the definition.

DR. GELPERIN: The numerator that Joy Mele used exactly matched the GSK adjudicated events. Karen Mahoney and I both reviewed GSK's pooled analysis and just determined and suggested to Joy that the events seemed appropriate to use as they were. So, we didn't change from GSK's decision.

In terms of serious and non-serious, it was the regulatory definition, which is that serious usually is a life-threatening doctor hospital admission. GSK chose to adjudicate events

as either myocardial ischemia or heart failure. For instance, and they can tell you this as well as we can, for non-serious events they reviewed the investigator verbatim term. So, according to their report, events with a code of chest pain were excluded from the numerator unless there was a specific indication that it was chest pain radiating to the left arm into the neck or a reason why it would be myocardial ischemia.

I think you are interested in what would happen with a non-serious case of dyspnea. That would have been determined by the GSK adjudicating committee, but chances are it would have been counted as a heart failure, non-serious event.

DR. ROSEN: Thank you. Dr. Schambelan?

DR. SCHAMBELAN: My question is focused--and perhaps this is for the sponsorB-on the ability of the ongoing trials, RECORD, BARI 2D, etc. to help reassure us ultimately about the safety of the product. Dr. Graham's comments here but particularly in the material he produced before the meeting raised questions about the power,

particularly of RECORD, and even the ethics of continuing that study, which he didn't say publicly but it is in the material. So, I wonder if you could tell us what your response to that is.

DR. COCCHETTO: Sure. Let me ask Nevine Zariffa to respond, please.

DR. ZARIFFA: Thank you. As you can imagine, we have been looking at this rather carefully, although our ability to interrogate the precise event rate in studies run by the NIH is not done through anything other than using protocol event rate assumptions. And, using conservative estimates, we believe that we would accumulate another 550 MACE events in addition to the 200 or so that we currently have and that will add substantially at completion of those studies to our ability to exclude effects or increases in the neighborhood of 20 percent.

DR. SCHAMBELAN: Are you talking about RECORD or about BARI 2D?

DR. ZARIFFA: BARI 2D, ACCORD, VADT, APPROACH, RECORD plus what is exactly on the docket

now, those 200 events of MACE that we have been discussing from the 28,000 patients involved in the trials.

DR. ROSEN: Thank you. Dr. Schade?

DR. SCHADE: Thank you. I would like to make a point for the committee and maybe for Dr. Graham from a clinical point of view. He had a slide this morning that argued that rosiglitazone had not shown any advantage towards macrovascular or microvascular complications.

I would like to address the microvascular complications for one minute. I would agree with him that we haven't seen a benefit of rosiglitazone towards microvascular complications. I would also argue that I hope we never do. The reason basically that I say that is that if you go back 15 years ago when we were doing diabetes control of complications trial there was an editorial in *Lancet* which strongly suggested that we quit this trial because everybody knew that glucose caused microvascular complications, and David Nathan wrote an editorial in response to the *Lancet* that

basically, yes, but these were retrospective survey kinds of studies and we really had no prospective studies. But since that time we do have the diabetes control and complications trial. We have two other similar studies in type 2 diabetes. So, I don't think anybody now questions that if you lower the hemoglobin A1c you will prevent, or at least delay significantly microvascular complications. That is eye disease, kidney disease and nerve disease.

So, I think that nobody right now would want to do that kind of trial because who would want to be in the control group? Nobody. So, it is really not appropriate to do that trial. I think we know that lowering the glucose reduces microvascular complications. So, I think we should not argue that rosiglitazone maybe should be taken off the market because there is no evidence that it reduces microvascular complications. I don't think we want to see that evidence. We really don't want to see it for any of the new anti-diabetic medications coming out, and I think that should not

be part of our argument.

DR. ROSEN: Thank you, Dr. Schade. I have a question for Dr. Mele, and that relates to the analysis of a subgroup, subgroup analysis in general but in particular the insulin plus rosi versus insulin alone. I guess my concern is, with those very wide confidence intervals, how confident are you that these subgroup analyses, especially with small numbers, are going to allow us to make any determination about patients at risk.

MS. MELE: Are you talking just about the insulin combination?

DR. ROSEN: Yes, just the insulin combination.

MS. MELE: Well, I actually feel pretty strongly about the insulin combination and not about any of the others because of the consistency of the results across all the endpoints and it didn't seem to matter how I looked at the data. For instance, if I looked at nitrate users in the insulin group where I could see a strong effect in a lot of the other meta-groups, when I looked at

the insulin group it didn't seem to matter whether I took out the nitrate users or not, and it did matter in the other groups. There were other things like that. If I would do subgroup analyses within that group, I would still see an effect, no matter what group of patients I would take out. So, I was looking at the robustness of that particular group and that is where my feeling about that group was.

DR. ROSEN: So, you would say of all the subgroup analyses you did, the one with insulin is the one that you are most confident about?

MS. MELE: Yes, I would.

DR. ROSEN: Dr. Fradkin?

DR. FRADKIN: I have a question for Dr. Nissen. I think I understood you to say in your presentation at the American Diabetes Association that it was, in fact, seeing a signal in DREAM that led you to do the meta-analysis. My understanding is that when you are trying to validate a signal generally you don't include the study that gave you the signal. I know the FDA and GSK, I guess,

didn't include DREAM in their meta-analysis and I wondered why you chose to do it.

DR. NISSEN: I think the reasons that the others didn't include it is it was done in pre-diabetic rather than diabetic patients, and I understand the reasons for that. We made a decision when we embarked upon this that we would look at all of the randomized, controlled data, and you always take the chance that if you apply a filter that says, well, we are going to include some studies but not include others that you will have an effect that is not desirable. So, we made a decision right from the top that we would look at every single clinical trial.

Now, it really turns out that it doesn't matter because the FDA did it one way and they got a 40 percent increased risk of ischemic events. We did it another way and we got a 40 percent increase. GSK did it their own way and they got a 31 percent increase. So, from my perspective, you know, cherry-picking the trials here is not at all the issue. The issue is that three different

groups, using three different approaches, and actually somewhat different endpoints--I mean, they used ischemic heart disease. We used myocardial infarction, and I want everyone to understand why we did that. We knew that these data were not adjudicated and we felt strongly that a myocardial infarction is an event that is a lot clearer, a lot less fuzzy than myocardial ischemia. So, at the outset we actually did this as a prespecified approach. And my own view of a meta-analysis is that that is what you should do. You should actually do a meta-analysis the same way you would do a randomized trial. You should determine your endpoint in advance, what your criteria for inclusion are going to be, and then go about doing it in an unvaried way. Some other speakers here suggested, well, why don't you look at all these other alternative approaches. We didn't do that because that is, in my view, improper data mining. We took a single approach and did it. Interestingly enough, no matter how you cut the data, you get this 30-40 percent increase in

myocardial ischemia.

DR. ROSEN: Thank you. Down at the end?

DR. STEMHAGEN: Yes, I am Annette Stemhagen. A couple of comments and a question for Dr. Dal Pan. But I thought one of the ground rules that the FDA started with was that we weren't going to be talking in detail about the Nissen study but talking about the data presented here. That is just an aside.

My question to Dr. Dal Pan is really that I would like a clarification on the FDA making and, in fact, I think encouraging a comparative analysis with pioglitazone sort of as a reason for rejecting rosiglitazone, under the circumstances that it is a meta-analysis that has not been reviewed by the FDA the way the GSK one was. So, it seems like you have got the GSK analysis and you were concerned about it and you re-analyzed it. Yet, we are hearing the Takeda one without your very careful re-analysis, as I understand it, that the committee was given the data only on the fly on a very few quick slides but we are asked to really put that as

part of our decision-making.

Then, the third is that, as I understand it from a comment and an article that was referenced as fact that was from a non-peer reviewB-at this point I believe the California Medicaid data has not gone through peer review but maybe I misunderstood that, but there are a lot of data here that are being discussed that we haven't seen before and it just seems a little contradictory. So, I would like some comments on that.

DR. DAL PAN: Sure, I would be happy to answer those questions for you. The easiest one I think is the California Medicaid. This is a study that Dr. Graham is doing with some colleagues outside of FDA who have access to California Medicaid data. This is a study that the team at FDA hasn't seen yet and I think Dr. Graham just chose to add those results to further his argument.

DR. STEMHAGEN: So, neither FDA nor peer review, internal peer review or external peer review on this data?

DR. DAL PAN: Internal peer review hasn't happened, no, that is correct. So, Dr. Graham was reporting what I believe are preliminary results. I think that is an important point to note, and he had no slides on that either.

You are correct, and I think I tried to make the point as to the others, that the pioglitazone data has not undergone formal FDA review. Those data have arrived much more recently. They will be undergoing formal FDA review.

With regard to your charge, your questions, the questions for the committee don't ask about comparison to pioglitazone. This was something that we were talking about in terms of how we think about the data, but your charge is not to compare rosiglitazone to pioglitazone. If you look at the questions--

DR. STEMHAGEN: I think that is a very helpful clarification. I am the industry representative and I would just like to make sure it is very clear what the questions are.

DR. DAL PAN: We are not asking you to make a comparison of pioglitazone to rosiglitazone in any way.

DR. ROSEN: Yes, the goal of this committee is really to analyze the results from the meta-analysis, to discuss the meta-analysis, the observational trials and the randomized trials.

DR. STEMHAGEN: I agree, but there seems to have been a lot of discussion about, well, maybe one of the things we need to think about is that there are alternative therapies, and one of the alternative therapies that is mentioned is data that we really haven't analyzed.

DR. ROSEN: Well, I am concerned about that because I think that that is in the public record or it has been noted. Even though there was no slide on it, we have never been exposed to that kind of data. So, I agree with your point and that probably is not something that we should consider at all. Dr. Kramer?

DR. KRAMER: Just further on that point, I read the bullet under question four as bringing

this up because it asks directly is there evidence that this risk is greater than other available therapies, and one of those therapies is pioglitazone. So, I think that our assumption in reading that question could well extend to pioglitazone and I think that should be clarified.

DR. ROSEN: Thank you. Let me just read question four so that everybody understands what it says. It says do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes? If yes, is there evidence that this risk is greater than other available therapies for the treatment of type 2 diabetes?

Unfortunately, we do not have any of the other data with pioglitazone to evaluate that second part of the question, which is actually a very important question. So, your point is well taken. Dr. Meyer?

DR. MEYER: Yes, I would just say that I believe the committee can form its definition of available data that is that first part of the question. So, you know, for instance, if you look

outside this direct head-to-head comparison within the class, across the class, we know for many of the agents that are commonly used for diabetes not a lot in this regard in the same way that is being examined for Avandia.

DR. ROSEN: I think we might need a little more clarification because I don't think that quite answers it. My understanding was that this was related to the therapies that are currently out there that we were given information about in our packet. Does it include the presentation of Dr. Graham in that data? Because I think this is actually a very relevant point when we come to deciding what to do with this drug.

DR. MEYER: First of all, let me be clear that the voting part of the question doesn't take in the relative aspect. The bullet underneath is a discussion point. Again, I think the committee can decide how to answer that.

DR. ROSEN: Great. Is everybody clear? Is the committee clear on that?

DR. KRAMER: Even if it is not in the vote,

it is in the public record so I think it should be clarified for the bullet.

DR. ROSEN: Dr. Teerlink?

DR. TEERLINK: Yes, I just want to reinforce something that Dr. Moss brought up. One of the advantages of kind of going last or later in the game is that most of my other questions have been addressed, but I think a message that the FDA and the sponsors need to hear is that this evaluation of safety is incredibly difficult and challenging, and to design studies where you emphasize time to first event for a safety issue is not appropriate and I think we really need to emphasize that data on all SAEs during the complete follow-up need to be pursued, and need to be actively pursued and that needs to be part of the requirements in terms of these either Phase 3 or Phase 4 type studies. I just want to reinforce something that Dr. Moss brought up very well but I think it is incredibly important.

DR. ROSEN: Dr. Parks, did you have a comment?

DR. PARKS: Yes, I actually wanted to just clarify on that bullet under question four. When the question was written by the agency, both in the Office of Surveillance and Epidemiology and the Office of New Drugs, it was with the understanding that the committee members would have these data, that is data not only for rosiglitazone but data with other agents, comparative studies, for you to make that kind of decision or weigh that into your response. I think that it puts you much at a disadvantage to consider the meta-analysis from pioglitazone without having seen the data, and actually I would say that it puts us at a disadvantage because we have not reviewed it either.

You also heard earlier by several speakers that we have some questions and concerns about the comparability of comparing pioglitazone meta-analysis to the rosiglitazone meta-analysis. Now, having said that, I recognize that this is in the public domain, but not having all the information I think that it is a bit risky to try

to weigh that evidence into determining question four.

DR. ROSEN: Thank you. Eric?

DR. HOLMBOE: I just want to follow-up a little bit on Dr. Teerlink's question. This is a question to the FDA. Given that there has been concern raised today that even the current randomized, controlled trials may not have sufficient power to detect the kind of signal at lower hazard ratios, what other plans does the FDA have with regard to observational or longitudinal type databases, such as registries or other things, to try to look at this issue? Because, you know, this is the fifth time I have sat in one of these difficult drug risk/benefit committees and this always comes up. I am just curious as to what is afoot to try to deal with some of these difficult power issues with regard to more longitudinal studies.

DR. DAL PAN: Well, the first thing we are going to do is take a look at the studies that we haven't analyzed all that carefully yet. I think

that is the first thing. We don't have a particular plan of studies yet, given that we don't know the outcome of this meeting or what regulatory action we will be taking. Though the outcome of this meeting may influence that, there is no particular plan at this point.

DR. ROSEN: Dr. Geller, do you have a comment?

DR. GELLER: This is a comment on the discussion, on how it has been going and what I am hearing. We have heard it said that the time to first event is insufficient and that is the data that have been collected. But with regard to question four, most of the trials are only six months in duration so that you couldn't have that data. I think that brings up the quality of the data that went into these many meta-analyses. Here I think we may be looking at an example where the quality of the analyses far exceeds the quality of the data.

DR. ROSEN: Yes, Dr. Van Belle?

DR. VAN BELLE: One of the points that was

raised was the observations with respect to second events. The PROactive study looked at people with prior cardiovascular disease. So, would that study provide some evidence with respect to Dr. Moss' question?

DR. ROSEN: Any comments? John?

DR. TEERLINK: Actually, so you bring up an additional point, or I think you are bringing up an additional point and it will be something I will address later as well. Most efficacy type studies are designed to actually purposely pick a low risk population in terms of adverse events. So, there are occasionally studies that have kind of these higher risk patient populations so you have the secondary instigation of an ischemic heart disease event. That is one issue.

The second issue is that when you are looking at safety within any of these patient populations having one ischemic event and, you know, if someone has a myocardial infarction, a revascularization, another myocardial infarction and another myocardial infarction, that, to me, is

more important than someone who has a first event for revascularization and that is it, and we are capturing that information and, yet, I think it is very relevant to the safety issues.

DR. ROSEN: I would like to ask the people on the telephone, Dr. Oakes in particular, if he has any comments of questions.

DR. OAKES: One, I guess, unrelated question to Joy Mele. This relates to page 12 in your review. You say studies were pooled in meta-groups and the analysis was stratified by meta-groups so that certain control arms were essentially counted twice in the overall analysis. I guess that statement bothered me a little and I would like you to explain particularly any effect that it might have had on the overall estimates and p values.

MS. MELE: Well, if I did an analysis stratifying on meta-groups, then the control group actually would be counted twice but in separate meta-groups. So, I just wanted to make that clear first. So, I saw that as less of an issue. Also,

when I did overall analysis where I stratified by study, then I dropped off those extra control arms.

DR. OAKES: So, it actually introduces a slight correlation in the estimates for the different comparisons but it doesn't affect the overall odds ratios.

MS. MELE: You know, there were only four studies that fell into that category and they were very small studies, monotherapy studies that were of short duration and usually had either no events or few events. So, it didn't really have any impact.

DR. OAKES: And the other comment which I was going to make later but maybe I will make now is just about the methodology of the meta-analysis. My understanding is that the method you used primarily, which keeps the zero events, is essentially the Mantel-Haenszel test in terms of determining significance, and that is the recognized method for determining the statistical significance of an association.

MS. MELE: Well, that is not the only

analysis I did. I did an exact test also--

DR. OAKES: But the exact test I guess would be even better--

MS. MELE: B-with a conditional maximum likelihood estimator.

DR. OAKES: But supposedly not any need to add corrections to the zero event--

MS. MELE: Right.

DR. OAKES:B-at least in determining the statistical significance of the association.

MS. MELE: Exactly, and the only time you saw the estimate from the Mantel-Haenszel with the correction was in the forest plots, but otherwise all my tables showed the conditional maximum likelihood estimates without corrections.

DR. OAKES: Thank you.

DR. ROSEN: Dr. Nelson?

DR. NELSON: Yes, I have an unrelated question also and I am not exactly sure who to address it to, perhaps Dr. Graham or perhaps to the sponsor, and this may go towards the biological plausibility issue as well. But one of the tenets

in toxicology is that the greater the dose, the greater the response. And, I don't know if any of the groups have ever tried to stratify the outcomes based on the dose of exposure.

MS. MELE: Actually, that is how I started my analyses. I looked at dose and, in fact, I saw the reverse. I saw a higher event rate with the lower dose than with the higher dose. But I looked at individual studies too because I wanted to make sure I could sort that out and make sure that there wasn't any indication whatsoever of a dose response and I didn't find any. I don't know if the sponsor wants to add to that.

DR. ROSEN: We have a comment from Dr. Walker.

DR. WALKER: Thank you. I mean, I think what is clear is that you do see a dose response with heart failure. You don't see a dose response with ischemia and myocardial infarction, and I think that reflects back to the plausibility question. There certainly is a possibility of TZDs causing fluid retention but we do not have a

plausible mechanism where TZDs would necessarily cause plaque rupture. If anything, the data goes in the other direction.

DR. HENNESSY: This is a question for Dr. Dal Pan or for Dr. Graham as well. In your presentation you seem to be putting forward the message that we have enough information today for us to vote that Avandia should no longer be on the market. Part of that decision has to do with the comparative safety and comparative effectiveness with other agents on the market. You made the point that a double standard for safety versus efficacy makes sense. I have also heard that we shouldn't have a double standard for withdrawing versus approving, although I think that a double standard there makes sense as well. I am getting around to my question.

My question is, given that there have been lots of data discussed here that haven't been thoroughly reviewed, whether you still think that we have enough information to make the decision that Avandia should no longer be available or

whether it would be more prudent to wait for some of these other data to come in and have a chance to analyze them in a more rigorous way.

DR. GRAHAM: Right. Regarding studies that are still out there waiting to be done, at the end of the day I don't think that they are going to give us the clarity that this committee would like, that any of us would like. ACCORD was not designed to answer the specific question of risk with rosiglitazone. BARI 2D was not designed to answer that question either. The slide that we were shown before shows that most of the patients that are in ACCORD that are getting rosiglitazone are also getting metformin. If metformin reduces cardiovascular risk, and there is a substantial amount of evidence in UKPDS and a number of other observational studies, if that is the case, then you have a mixing of effects. If, let's say for example, rosiglitazone increases the effect at the end of the day I don't think they are going to give you the clarity.

The cost of waiting for confusion at the

end where you are going to be inconclusive again is whatever the toxicity is. At some point you are going to have to make a decision based on data that is not perfect, and you are going to have to sort of weigh what is available and say, well, given this, what makes sense.

Now, regarding pioglitazone data that hasn't been fully reviewed by FDA, I think it is important that it be noted that Dr. Dal Pan and I, very early in our evaluation of this, saw the pioglitazone meta-analysis as the single most important piece of additional data that was needed in preparation for this advisory committee meeting. We were assured--we were promised by the Office of New Drugs that that analysis would be done. Then, subsequently we learned that they were going to outsourced it to Takeda to do so FDA said we can't find a statistician. We have over 100 statisticians at FDA and we can't find one to work on this, to give it a high priority to do the analysis so we have to outsourced it to Takeda. Then, we can't get somebody to honcho the analysis

and tell Takeda to do the analysis so we will ask a medical officer who is retired from FDA now, but who is a special government employee, we will ask him to come out of retirement and sort of orchestrate Takeda's analysis of this issue. Then he concludes that it is too complex to get done in a short amount of time so at the end of the day then I am sort of faced with a dilemma. Do I present the evidence that we have in-house that was reviewed by FDA that was not reviewed the same way as Joy Mele doing the rosiglitazone meta-analysis, or keep silent about that and not breathe a word of it?

So, I presented it, and I presented it for a couple of reasons. One, I believe that the Takeda analysis of their meta-analysis, their pooled analysis, was a much more rigorous example of that type of work than the original work that GSK submitted to us. The final conclusions that Joy Mele reached compared to the rosiglitazone analysis the company did is qualitatively no different. The coronary heart disease risk is

increased. I don't believe that the coronary heart disease risk from the meta-analysis from pioglitazone is going to change a whole lot. Maybe it will. But we also have PROactive. PROactive was a study done in a very high risk, sensitive population. So, these are people that you would think that if pioglitazone was going to increase cardiovascular risk-it is like a strong puff of wind should knock those people over the edge and you should have an event and, instead, they took a few steps back from the ledge.

So in answer--long-winded and I am sorry about that-to your question is that I think that we do have sufficient evidence to draw a conclusion that in general it appears that rosiglitazone has a cardiovascular risk that pioglitazone does not have. Is it definitive? No. Is it more likely than not? Yes. That comes with a population cost, and that is why I talked about the asymmetry of the costs of a wrong decision.

DR. ROSEN: Dr. Dal Pan?

MS MELE: I would like to defend my Office

of Biostatistics and just mention that we are on track to do the pioglitazone analysis, but the date of this meeting was changed drastically and that is why it wasn't done at this time.

DR. ROSEN: Right, originally it was November and then September. Dr. Dal Pan?

DR. DAL PAN: I just wanted to make a few comments on this issue. I think several members of the committee have raised legitimate points about presenting pioglitazone data. There are two choices. You either present it or you don't. I think we felt, David and I felt, that this was a clinically relevant issue and so, given what we knew about PROactive, which has been carefully reviewed by the FDA, we would present some of the early findings from the pioglitazone data with the caveat that I mentioned, that these have to undergo further FDA review. But, as David said, we still do have the PROactive data that have been carefully reviewed by FDA.

There were changes in the schedule that necessitated the meeting without the full FDA

review of the pioglitazone meta-analysis data and even some of the GSK data that we are presenting that GSK has put in their packet that we haven't had the time to analyze as well. The PharMetrics study and some of the others, we haven't had time to analyze them quite as well. So, it works both ways.

But this isn't about rosiglitazone versus pioglitazone. It is about a total look at the risk of myocardial ischemia with rosiglitazone and how the pieces of data fall out that, given their uncertainty, would lead one to make one conclusion over another.

DR. ROSEN: Dr. Henderson and then Dr. Teerlink.

DR. HENDERSON: This is a question for either Dr. Graham or Dr. Dal Pan. This afternoon we heard from patients and physicians. One of the themes that we heard over and over again is that we need lots of tools in our toolbox to fight diabetes. Don't take this tool away from us. If we took this off the market, we would be taking one

of the tools out of the toolbox. How would you respond to that to a patient?

DR. DAL PAN: We take these decisions very seriously. One of the things I said in my remarks earlier in the day was that I recognize the burden of diabetes in the United States and the need for glycemic control and the need for treatment. But if the risk of cardiovascular disease, if the risk of excess myocardial infarction is 40 percent above the background, I think that even Dr. Meyer said that this is something that we would take very, very seriously. Cardiovascular disease being the leading cause of death amongst diabetes, to have a treatment that does that is something that just didn't make sense to me.

DR. GRAHAM: I would add to that. It is true that we could use much more effective therapies for diabetes. There is no question about that. But there are two things. You had individuals speaking about their personal experience and, as I said in my own presentation, there is no question that you can find individual

patients for whom rosiglitazone is the only drug that gives them glycemic control. They tried other drugs and they failed. But FDA can't base regulation on the experience of isolated individuals. It has to base it on a population, looking at what is most likely to be the outcome. When we look at that, it doesn't profit the population of patients in the United States with diabetes to have a tool in the toolbox that increases their coronary heart disease risk by 20 percent, 40 percent or 70 percent. It doesn't profit them.

There may be an isolated individual here and there; there may be user groups on the Internet, and I am sure there are, who say this drug saved their life. But the fact is that when you look at a population level it doesn't profit them, and that is the perspective that we are looking at. What I was trying to get at the end of the day is how many people does rosiglitazone keep out of the hospital or out of the cemetery because of coronary heart disease risk? And, how many

people is it more likely than not putting into the hospital or putting into a cemetery because of coronary heart disease risk? What I see is that it looks like there is no evidence it is keeping people out and there is a substantial body of evidence that it is putting them in.

Now, getting to the pioglitazone question, I don't see how this committee could consider whether or not rosiglitazone stays on the market or not without considering how this drug stacks up against pioglitazone. So, that was another motivation behind our decision to present what we did about pioglitazone at this meeting.

DR. ROSEN: Dr. Teerlink and then Dr. Savage.

DR. TEERLINK: So, Dr. Dal Pan gave two options in terms of what the decision might be, and I would like to suggest that there was actually a third option, and that is to either have the political will to schedule a meeting when the available data is there and completed and actually have us be able to deliberate on the full set of

data and come to a meaningful decision, or have the intellectual integrity to not present data that we don't know what to do with, and I think that is a third option that should have been more strongly considered.

DR. ROSEN: Dr. Savage?

DR. SAVAGE: I think there is another issue that seems to have been passed over, and that is that there is a fairly large spectrum of risk between someone who is pre-diabetic or very early diabetic and someone who has had the disease for 20 years. So, when we talk about the risk as if it is the same for someone whose fasting glucose is 127 versus 300 with a 20-year history, we are talking about two very different things.

So, when we are trying to weigh the value of a TZDB-I don't think you have given us enough information to really distinguish whether one is really definitively better than the other, but if we are trying to weigh the value of a TZD it could be that the use of these drugs to either prevent the development of diabetes or slow the progression

of diabetes and the loss of beta-cell responsiveness could more than offset a very slight increase in absolute risk of cardiovascular disease at that end of the spectrum. At the other end of the spectrum where you are adding rosiglitazone to insulin therapy the results could be completely different. It could be an unjustifiable increased risk.

DR. ROSEN: Dr. Kramer, and then I want to make some comments because I think we have to move this along. Independent of the meeting date and when it should be, we have to get going. Dr. Kramer?

DR. KRAMER: Just in the spirit of having some discussion about this, I would like to follow-up on what Dr. Geller said in terms of the quality of the analyses being better than the quality of the data.

I think we are frequently forgetting that the primary data upon which people are suggesting this drug be taken off the market is serious adverse event reporting in clinical trials,

non-standard definitions dependent on the investigator observing the event and recording the event both in their record and for the sponsor. And, I think that is quite different than meta-analyses of trials where you actually have a standard definition of an endpoint. So, I just don't want to forget that.

And, I would like to point out the fact that neither Dr. Graham nor Dr. Dal Pan addressed slide number 22, presented by Karen Mahoney, that talked about the differences between the rosiglitazone and pioglitazone clinical trial protocols that would raise some questions about this superficial comparison that we have been asked to do today in light of being responsible by not excluding data.

DR. ROSEN: That is an important question, if you could respond, Dr. Dal Pan.

DR. DAL PAN: I think the point was that there are differences between these meta-analyses and we have to look at them. I think the reason we put them in is because we had the PROactive data

that has been well reviewed and this was consistent with that. I take your point that these re very different meta-analyses and it was either show you what we have and caveat it, or not show it at all. It was just one of the two. We made the decision that we made and I am hearing it wasn't the right one.

DR. KRAMER: But it was presented as if we took rosiglitazone off the market we would have this other agent as a perfectly appropriate alternative. So, that is going beyond what I hear you saying.

DR. DAL PAN: That wasn't my intention in saying anything about rosiglitazone versus pioglitazone.

DR. ROSEN: Thank you, Dr. Kramer. Unless there are any other comments, I would like to start the second part of this, which means that I am going to ask individuals to comment on the first three issues, which are the quality of the meta-analysis, the quality of the observational studies and the quality of the randomized trials.

I am going to start with Dr. Stemhagen, if she doesn't mind being the lead off and I will come back to Steve at the end, and just ask her for any comments, concerns or issues lumping all three together. This is the preliminary sort of walk-up to the vote and you can say as little or as much as you want. But let's limit it to the first three questions that we have been asked to comment on, and those are really related to data quality and analysis.

DR. STEMHAGEN: I would be happy to do so but I know Dr. Ryder needs to leave before I do so I am wondering if you want to start with him.

DR. ROSEN: I just wanted to start with the temporary voting members, if that is okay. Oh, you are not a voting member?

DR. STEMHAGEN: I am not a voting member.

DR. ROSEN: Okay, Dr. Ryder can go first and then Dr. Stemhagen.

DR. RYDER: Thank you, Dr. Rosen. Today's discussion has really brought out a number of very important issues. I think that most of them, if

not all of them or many of them have already been raised. It is very important to consider and comment on design and analytical and review concerns and standards, and on the application of these standards best design analytical review practice to all data presented for review. These include many things that have been mentioned, continuity corrections, short-term, long-term, trial result validation concerns and people raising that in a number of different presentations. I think it is important for the committee to consider that guidance in this area would help improve risk/benefit reviews, provide the best data, allow discussion to focus on really the key issue, which is clinical relevance and action.

DR. ROSEN: Thank you, Dr. Ryder. Dr. Stemhagen?

DR. STEMHAGEN: As an epidemiologist, most of my comments are about the observational study. They look to me, from the data we received and the reports, that they were very carefully done, very high quality. They used propensity scores and

other things to try to match people. A lot of the concerns always about observational studies are that there is selection bias and confounding. You certainly can't exclude that. That is always a problem with observational data. But they very carefully thought out ways to try and control for that.

So, I think the evidence in the observational study is very powerful and I think it is not getting as much credit as it probably should. That is my one comment.

My other comment is concern about the long-term studies. I think we have heard a lot about the need to really look at long-term effects. So many of the data in the meta-analysis were these short-term six-month studies because they were looking at efficacy. But I am concerned, and I think it was discussed in some of the briefing documents, that because of the great publicity now there are a lot of people who are dropping out of those studies and it may be very difficult to continue enrolling or continue to get them