Official Transcript

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Hilton Hotel
8727 Colesville Road
Silver Spring, MD 20910

April 1, 2009
8:00 a.m. to 5:00 p.m.

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AGENDA

- On April 1 and 2, 2009, two different new drug applications (NDAs), proposed for the treatment of hyperglycemia in adults with type 2 diabetes mellitus will be discussed.
- On April 1, 2009, the committee will discuss NDA 22-350, Saxagliptin tablets, Bristol-Myers Squibb.
- On April 2, 2009, the committee will discuss NDA 22-341, Liraglutide injection, Novo Nordisk, Inc.

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ROSTER 2009

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Updated: February 25, 2009

Endocrinologic and Metabolic Drugs Advisory Committee
Hilton Hotel, Washington DC-Silver Spring
Silver Spring, Maryland
April 1, 2009

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CALL TO ORDER AND INTRODUCTIONS

KENNETH BURMAN, M.D.

DR. TRAN: Good morning. Before we start, I just want to remind everyone again that even though this is a public meeting, for the public and everyone in the audience, please do not cross over the rope to approach the panel members at any time during the meeting today including the breaks. Thank you.

DR. BURMAN: Good morning. I would like first to remind everyone present to please silence your cell phones, Blackberries and other devices if you have not already done so. I would also like to identify the FDA press contact, Ms. Karen Reilly, who is standing on my left. Thank you very much. I would like now to have introductions by members and consultants around the table. Dr. Parks, would you mind starting?

DR. PARKS: Mary Parks, Director of Division of Metabolism and Endocrinology, FDA.

DR. JOFFE: Hylton Joffe, Lead Medical Officer for the diabetes drug group in FDA.

DR. LOWY: Naomi Lowy, Medical Officer, Division of Metabolism and Endocrinology Products.

DR. KONSTAM: Mark Konstam, Tufts Medical Center, Cardiology.

DR. HENDERSON: Jessica Henderson, Consumer Representative.

MR PROSCHAN: Michael Proschan, Statistician at the National Institute of Allergy and Infectious Diseases.

DR. FLEGAL: Kathrine Flegal, Epidemiologist at the Centers for Disease Control and Prevention.

DR. BURMAN: Ken Burman, Chief of Endocrinology at the Washington Hospital Centre and Professor of Medicine at Georgetown University in Washington DC.

DR. TRAN: Paul Tran, Designated Federal Official for the EMDAC Advisory committee.

DR. LEVITSKY: Lynne Levitsky, pediatric endocrinology, Massachusetts General Hospital.

DR. WYNE: Kathleen Wyne, endocrinologist, the Methodist Hospital Research Institute, Weill Cornell Medical College, Houston, Texas.

DR. TEERLINK: John Teerlink, Professor of Medicine, University of California, San Francisco and cardiologist at San Francisco VA Medical Center.

DR. KILLION: I am Rebecca Killion; I am a patient representative and a type 1 diabetic.

DR. SAVAGE: Peter Savage. I am an endocrinologist at NIDDK and prior to being there for the last year and a half, I was at the NHLBI.

DR. LESAR: Timothy Lesar, Director of Clinical Pharmacy Services, Albany, New York and New Drug Safety and Risk Management Committee.

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

DR. FELNER: Eric Felner, pediatric endocrinologist at Emory University in Atlanta.

DR. ROSEBRAUGH: Curtis Rosebraugh, Director, Office of Drug Evaluation.

DR. BURMAN: For a topic, such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and individuals can express his/her views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and The Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. A press conference will be held in the Sovereign Room immediately following the meting today. Also the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

CONFLICT OF INTEREST STATEMENT

PAUL TRAN, R.PH.

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

The following information on the status of this Committee in compliance with the Federal ethics and conflict of interest law covered by, but not limited to, those found at 18 U.S.C. §208 and §712 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this Committee are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. §208, Congress has authorized FDA to grant waivers to Special Government Employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under §712 of the Food and Drug &Cosmetic Act, Congress has authorized FDA to grant waivers to Special Government Employees and regular Government employees with potential financial conflicts, when necessary, to afford the Committee essential expertise.

Related to the discussion of today's meeting, the members and temporary voting members of this Committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses and minor children and, for the purposes of 18 U.S.C. §208, their employers. These interests may include investment; consulting; expert witness testimony; contracts/grants/CRDAs; teaching/speaking/writing; patent and royalties; and primary employment.

Today's agenda involves discussions of Saxagliptin tablets, Sponsored by Bristol-Myers Squibb, for the treatment of hyperglycemia in adults with type 2 diabetes mellitus. This issue is a particular matter involving specific parties.

Based on the agenda for today's meeting all financial interests reported by the Committee members and temporary voting members it has been determined that our interests in firms regulated by the Center for Drug Evaluation and Research present no potential for conflict of interest.

With respect to FDA's industry representative, we would like to disclose that Dr. Rick Veltri is serving as the non-voting industry representative, acting on behalf of our regulated industry. Dr. Veltri's role at this meeting is to represent industry in general and not any one particular company. Dr. Veltri is employed by Schering-Plough.

We would like to remind members and temporary voting members that if the discussion involves any other products or fillers not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

DR. BURMAN: Eric, good morning. We just introduced ourselves and maybe, would you be kind enough to do that as well?

DR. FELNER: My name is Eric Felner. I'm a Pediatric Endocrinologist at Emory University.

DR. BURMAN: Thank you. We will now proceed with our first presentation from the FDA by Dr. Hylton Joffe.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

INTRODUCTION AND BACKGROUND

HYLTON JOFFE, M.D., M.M.SC.

Good morning, Dr. Burman, Members of the Advisory Committee, Ladies and Gentlemen. My name is Hylton Joffe. I'm the Lead Medical Officer for the Diabetes Drug Group at FDA. I would like to welcome everybody to this two-day Advisory Committee meeting where we will be discussing two new treatments that have been developed for type 2 diabetes.

Today we will focus exclusively on Saxagliptin, a product from Bristol-Myers Squibb. Tomorrow we will focus exclusively on Liraglutide, a product from Novo Nordisk. What I would like to do in the next 30 minutes or so is summarize the objectives of this two-day advisory committee meeting, also present an overview of the agenda for the two days. I would then like to briefly touch on the mechanism by which Saxagliptin and Liraglutide improve glucose control in patients with diabetes.

As you will soon see, the main focus of this two-day advisory committee meeting is to evaluate whether these two products have provided adequate evidence of cardiovascular safety to support marketing. For this reason, we will revisit the July 2008 advisory committee meeting which discussed Cardiovascular Assessment in the Pre-approval and Post-approval Settings for Drugs Developed for Type 2 Diabetes, and we will also discuss our final guidance published December 2008 that talks about cardiovascular assessment for new diabetes products. After that we will turn to the Saxagliptin and Liraglutide new drug applications and what we will do is we will give an overview of the cardiovascular analyses that were requested by FDA, some important considerations for the panel to bear in mind, and then we will end with discussion points and voting questions related to cardiovascular safety.

The objective for today's meeting is, as I said, to discuss Saxagliptin and specifically to discuss whether there is adequate evidence of cardiovascular safety to support marketing. Tomorrow, we will turn to Liraglutide and we will ask that exact same question. Is there adequate evidence of cardiovascular safety to support marketing? For Liraglutide, there also will be discussion and voting related to non-clinical thyroid C-cell tumors as well as several cases of papillary thyroid cancer reported in the development program. That's all that I will say about those topics for today, we will revisit them tomorrow.

The agenda for both days is quite similar. You are hearing my presentation now, which applies to both days. Then the applicants will each have a chance on each day to present their data and then they will field questions from the advisory panel. After that you will hear FDA presentations. Today you will hear from our clinical reviewer, Dr. Naomi Lowy, and our biostatistician, Ms. Joy Mele. Tomorrow you will hear from our non-clinical reviewer, Dr. Anthony Parella, our clinical reviewer, Dr. Karen Mahoney, and another biostatistician Dr. Janice Derr.

After the FDA presentations there will be opportunity again for the Advisory Committee Panel to question FDA. There will be an open public hearing today. There was originally one scheduled for both days but we didn't receive any speaking request for day two, so there will be no open public hearing tomorrow. Then both the applicant and FDA can field questions from the Advisory Panel and then the Advisory Panel will have their discussion and voting.

Let's turn briefly to the mechanism by which these two therapies improve glucose control in diabetes. To do this, we first need to speak about GLP-1 (Glucagon-like peptide-1). This is a hormone that's released from the small intestine during meals.

GLP-1 stimulates Insulin release from the pancreas in a glucose-dependent manner, and because it needs glucose around to have its effect the risk of hypoglycemia is minimized when these types of agents are used by themselves. GLP-1 also slows gastric emptying and reduces inappropriate post-meal glucagon release.

Interestingly, patients with type 2 diabetes have a reduced GLP-1 response to meal but a preserved Insulin response to GLP-1 and this is the reason why GLP-1 based therapies are thought to have utility in this condition. The problem is it would be very difficult to give endogenous GLP-1, or GLP-1 that's identical to endogenous GLP-1, to patients except perhaps with a continuous infusion. That's because GLP-1 has a very short half-life, on the order of less than two minutes. That's because of rapid degradation by a ubiquitous enzyme known as dipeptidyl-peptidase 4 (DPP-4).

Currently, there are two approaches to GLP-1 based therapies for type 2 diabetes; either you could slow the degradation of endogenous GLP-1 using an inhibitor to that enzyme, an inhibitor to DPP-4, Saxagliptin is an example of this, or you could administer pharmacological GLP-1 that is resistant to DPP-4 degradation and therefore has a longer half-life. Liraglutide which we will be discussing tomorrow is an example of that mechanism. As I mentioned, Saxagliptin is a DPP-4 inhibitor. It's administered orally; the applicant is proposing once daily dosing. The only other approved DPP-4 inhibitor is Januvia or sitagliptin, which are also administered orally and also dosed once daily and there are other DPP-4 inhibitors under development.

Liraglutide, which we are discussing tomorrow, is a GLP-1 agonist. Because it's a protein-based therapy, it cannot be given orally so it's administered subcutaneously, and the applicant is proposing once daily dosing. The only other FDA approved GLP-1 agonist is Byetta (exenatide), which is also administered subcutaneously

but is dosed twice daily. There are other GLP-1 agonists, including longer acting formulations, under development.

I would now like to turn to our July 2008 Advisory Committee meeting. At this meeting we discussed the Cardiovascular Assessment in the Pre-approval and Post-approval Settings for Drugs and Biologics Developed to Treat Type 2 Diabetes. We heard presentations by experts in the fields of endocrinology and cardiology. Then our advisory panel discussed and voted on this issue. This panel was comprised of endocrinologists, diabetologists, cardiologists, statisticians, and drug safety experts.

At the end of this two-day meeting, the panel was asked to vote on the following questions: It should be assumed that an anti-diabetic therapy with a concerning cardiovascular safety signal during phase 2/phase 3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk? Of the 16 voting members, 14 voted yes. The transcript from this two-day meeting is shown on the link on the bottom of the slide where you can also read the rationale behind the votes.

For a few months after the July 2008 Advisory Committee meeting, FDA had internal deliberations considering the discussions that had taken place at that meeting as well as other data and subsequently published in December a final guidance entitled, 'Evaluating Cardiovascular Risk in New Anti-Diabetic Therapies to Treat Type 2 Diabetes'. I would now like to spend a few minutes talking about this guidance because it bears directly on what we will be discussing today. For those who are not aware, a guidance document is basically a document that describes FDA's current thinking on a particular topic and provides recommendations on that topic.

Key points from the diabetes cardiovascular guidance are as follows. It reaffirms hemoglobin A1c as the primary efficacy end-point for glucose reduction but also notes vulnerability of patients with diabetes to cardiovascular disease, which is the leading cause of mortality in this patient population. It asks Sponsors to demonstrate that new therapies for type 2 diabetes do not unacceptably increase cardiovascular risk. FDA has also publicly stated that, 'we would like to see evidence of cardiovascular safety for those unapproved therapies that either had already completed their development program or were in late stages of the development program at the time the guidance was issued'. Note this guidance does not discuss cardiovascular assessment for already approved treatments for type 2 diabetes; this will be addressed separately in the near future.

Key recommendations from the guidance are as follows. The guidance states that applicants should set up an independent committee to prospectively and blindly adjudicate major cardiovascular events. It recommends that the phase 2/phase 3 development plan be designed to permit a valid pre-specified meta-analysis of major cardiovascular events. It recommends that trials include patients at increased risk for cardiovascular disease, such as those with longstanding diabetes, renal impairment or advanced age. It also notes that trial duration should be longer than the typical six-month core Phase 3 trials used in the past for seeking approval for type 2 diabetes products and a longer duration would ensure that a sufficient number of cardiovascular events are accrued. Also provide long-term data for these chronically used therapies.

The guidance then goes on to explain how to quantify the cardiovascular risk of a new investigational agent. Basically it asks applicants to compare the incidence of major cardiovascular events occurring with an investigational drug to the incidence of major cardiovascular events occurring with comparator. It recommends that applicants

compute the point estimate for the risk ratio comparing investigational drug to comparator and also the 95% confidence interval for this risk ratio.

We then turn to the upper bound of this 95% confidence interval because the upper bound represents the "worst case" potential for increased cardiovascular risk based on a combined analysis across studies, and we set some criterion as to what that upper bound should be. The numbers, we will talk about in a moment, are 1.3 and 1.8. For example, an upper bound of 1.8 says that the estimated increased risk of cardiovascular events with an investigational drug is no worse than 1.8 times the risk with comparative.

Let's take a closer look at these two numbers, if the upper bound of this 95% confidence interval for the risk ratio is greater than 1.8, the guidance states that there would be inadequate evidence of cardiovascular safety to support marketing. If the upper bound falls less than 1.8 and there are no other approvability issues, the drug would be able to be approved but the drug may need a post-marketing required cardiovascular trial to definitively address cardiovascular safety. The cut point for this decision is 1.3. If the upper bound of the risk ratio is between 1.3 and 1.8 post-marketing cardiovascular trials would be needed to show definitively that the upper bound is less than 1.3. If the upper bound for this risk ratio is less than 1.3 and the drug can otherwise be approved, post-marketing cardiovascular trials generally will not be necessary. These upper bounds of 1.3 and 1.8 assume a reassuring point estimate.

I would now like to turn to the cardiovascular analyses that FDA requested of the applicants. Initially Bristol-Myers Squibb and Novo Nordisk were asked to conduct cardiovascular analyses and they use different approaches and different methodologies to analyze cardiovascular events. To create a more uniform approach

FDA requested that both applicants re-analyze their data and we specified the types of statistical analyses we would want to be used, the patient populations on which these statistical tests should be done, and what the endpoints should be. I would like to walk you through all of that in the next few minutes.

First the FDA asked that these cardiovascular safety analyses be conducted on two treatment periods. The first treatment period would be the randomized controlled periods for all completed phase 2/phase 3 trials up until the primary efficacy time point for hemoglobin A1c. For drugs developed for type 2 diabetes, these phase 3 trials are typically 24 weeks in duration. For a second treatment period we wanted applicants to also investigate cardiovascular safety including the patients who continued beyond the primary hemoglobin A1c time point provided that the data after this time point was controlled and remained randomized.

Let's look at what these treatment periods are for Saxagliptin for today and then for Liraglutide for tomorrow. That first treatment period is called the short-term period for Saxagliptin; again this is the typical 24-week core Phase 3 trials for type 2 diabetes products. The second treatment period is called the short-term and the long-term periods. Patients entered the long-term period after either completing the short-term period or upon requiring glycemic rescue sometime during the short-term period. This long-term period was double blind, patients remained on their original randomized treatment and these periods were non-voluntary. In other words, patients can't be asked, do you want to continue in this extension or not, patients did continue.

For Liraglutide, the two treatment periods are called "Population A" and "Population B". Again "Population A" is that typical 24-week treatment period. "Population B" includes patients who have continued beyond their treatment period in

extension studies. These extension studies were un-blinded but patients again remained on original randomized treatment and these extensions were voluntary - patients had the option of whether they wanted to continue or not. Patients in either "Population A" or "B" requiring glycemic rescue were withdrawn from the study.

I would now like to turn to the endpoints we used for the cardiovascular analyses and to do this I would like to give a little background on MedDRA. MedDRA stands for the Medical Dictionary for Regulatory Activities; it was developed by the International Conference on Harmonization (ICH). The ICH is involved in harmonizing requirements for drug development across the United States, European Union and Japan, and in a way to improve efficiency and reduce redundancy. MedDRA is what drug applicants use to code adverse events occurring during their clinical trials. An investigator can report the same adverse event in many different ways and it would be very impractical to try and use these verbatim investigated terms to tabulate the incidence of various adverse events.

There are coders who are trained in MedDRA who review the investigated verbatim terms and match them to what is known as the lowest level term in MedDRA. Each lowest level term is automatically linked to what is known as a preferred term and then when analyses of adverse events are done we use these preferred terms, which represents single medical entities. So, as an example, a patient can present with an arrhythmia and one investigator might report that as an arrhythmia, another might report it as a dysrhythmia. The arrhythmia would get coded to the arrhythmia lowest level term, dysrhythmia would get coded to the dysrhythmia lower level term, but both those level terms will code to the preferred term of arrhythmia. This is kind of a way of standardizing the terms that we will be using for analyses.

Now, because of MedDRA's size and complexity you can imagine that different users could select different sets of preferred terms when they are trying to retrieve cases related to a particular safety issue. To try and get around this, the MedDRA folks have developed what is known as standardized MedDRA queries, which is a grouping of preferred terms potentially related to a defined medical condition of interest, and SMQs have been developed to standardize the sets of preferred terms that should be included when evaluating a particular safety signal. So let's take an example. The myocardial infarction SMQ, and here I am working of a MedDRA version 11.1, consists of 30 preferred terms.

Four examples are shown on the slide; acute myocardial infarction, coronary artery occlusion, blood creatine phosphokinase increase, and electrocardiogram Q wave abnormal. So if a patient was reported to have experienced any of these 30 preferred terms they would be counted in this myocardial infarction SMQ and would be counted as having had a myocardial infarction.

Now, it's important to realize that although some of these preferred terms could be consistent with myocardial infarction, there may be another explanation in some patients. Take, for example, blood creatine phosphokinase increase. That could be due to exercise, trauma, and medications. In other words, conditions not related to myocardial necrosis.

With that background, I want to now talk about the two cardiovascular safety endpoints that FDA requested. When I use the term MACE, here that's shorthand for Major Adverse Cardiovascular Events. There is a broad SMQ MACE and a custom SMQ MACE. The broad SMQ MACE is a composite of cardiovascular death, preferred

terms from the myocardial infarction SMQ, and preferred terms from the central nervous system hemorrhages and cerebrovascular accidents SMQ.

Custom MACE refers to a subset of preferred terms from SMQ MACE that is considered more likely to represent events of myocardial infarction and stroke, as reported by investigators. How do we come up with a custom MACE? Well, a panel of three FDA clinical reviewers independently reviewed all the preferred terms in the SMQ MACE and they did so with the following question in mind. If I had a patient who actually had a myocardial infarction or stroke, is this a preferred term that I might actually have chosen for such an event?

The three reviewers did this independently, they didn't take into account what actual events had occurred, and then they regrouped, compared their custom lists and reached unanimous agreement on which term should and should not be included in the custom MACE. It's important to realize though that this custom MACE is not the same as post-hoc adjudication. The reviewers looked at preferred terms, not at the data behind the preferred terms. In a few slides later I will explain why post-hoc adjudication was not conducted for these clinical programs.

Let's give you an example of SMQ MACE versus custom MACE and the full list of the preferred terms in both endpoints is included in your briefing packets. As you can see all the terms on this slide are in the SMQ MACE, but only three are in the custom MACE. Take, for example, coronary artery occlusion. This may simply represent a stable fixed coronary defect, and doesn't necessarily imply an acute event, for that reason it's not included in custom MACE. Whereas coronary artery thrombosis does imply an acute event and is included in custom MACE. The preferred term infarction could be anywhere in the body, could be in the bowel, could be in the legs, and so

infarction is included is SMQ MACE but not in custom MACE. Whereas, myocardial infarction or silent myocardial infarction are included in both.

A quick word on the statistical analysis for these cardiovascular safety analyses and you will hear more about this from our statisticians over the course of the two days. First, FDA requested that results for these cardiovascular analyses be stratified by study. This preserves randomization and is particularly important when there is unequal randomization in a study. FDA also requested that an exact method be used for at least one analysis, and you will hear from the biostatisticians the value in using these techniques later today and tomorrow. As you can see FDA requested multiple analyses, two treatment periods, two endpoints, multiple comparators in some cases, various statistical methodologies. The goal of these multiple analyses was to look at the data in different ways to assist consistency of results.

Importantly, FDA used the same statistical approach for Saxagliptin, which you are hearing today, and Liraglutide, which you will hear about tomorrow. You may notice that presentations differ slightly, and that's because FDA picked the subset of analysis that we feel best represents cardiovascular risk for each of the products.

A few important considerations for the panel during their deliberations today and while they are hearing the discussions over the course of the day - The Saxagliptin and Liraglutide new drug applications were submitted to FDA prior to publication of the cardiovascular guidance. In fact, they were both submitted to FDA prior to the July 2008 advisory committee meeting. These programs were not prospectively designed for systematic measurement of cardiovascular risk. Cardiovascular event rates were low. There were no pre-specified definitions for major cardiovascular events of interest. For example, these programs didn't say that for an

event to be classified as a myocardial infarction it would need to meet criteria A, B, C, and D.

The analysis you will be hearing about that FDA and the applicant conducted are post-hoc analyses based on MedDRA preferred terms. There was no prospect of adjudication of cardiovascular events, and there was no prospect of adjudication either. Post-hoc adjudication was not conducted because many events had insufficient information for adjudication, getting back to this issue that these programs were not pre-specified to measure cardiovascular risk, and therefore they were not setup to always collect all the necessary information needed to definitively say whether event was due to a cardiovascular event of interest or not.

As I mentioned before, FDA used the uniform approach for Saxagliptin and Liraglutide to assist cardiovascular safety, but it's important that each application be evaluated on its own merits. Today you will hear about Saxagliptin and get to vote on Saxagliptin. Tomorrow you will hear about Liraglutide and get to vote on Liraglutide. These development programs differed and cross program comparison should not be performed.

I would now like to end with the discussion points that the panel will be asked to talk about toward the end of the day, and also the voting questions. I'm presenting them now to provide a framework for the panel as they hear presentations over the course of the day, so they can see the types of information FDA would like to obtain. So, the four discussion points on this slide apply both to Liraglutide and to Saxagliptin, which you are hearing about today. We would like the committee to discuss whether the low cardiovascular event rates, the endpoints, and the post-hoc analyses permit a reliable assessment of cardiovascular safety.

We would like to hear from the committee if there are suggestions for improving the endpoints and analyses that we may apply to phase 3 programs that either were completed or near completion when the cardiovascular guidance was issued. We would also like the committee to discuss the adequacy of the statistical methods for measuring sensitivity of the results to analytical method.

There are two other discussion points; one specific to Saxagliptin for today and one specific for Liraglutide for tomorrow. The Saxagliptin specific discussion point asks the committee to discuss whether the trial designs affect interpretation of cardiovascular results for the short-term period and for the combined short-term and long-term periods. For Liraglutide tomorrow, you will hear subgroup analyses comparing cardiovascular safety with Liraglutide to placebo and to active comparator. Of note, the primary comparison of interest for FDA is cardiovascular safety of Liraglutide compared to total comparator, and the guidance doesn't talk about applying these criteria of 1.3 or 1.8 to subgroup analyses.

Nonetheless, we would like the committee to discuss the relevance of the differences noted by type of comparator and the role that these separate types of comparatives could play in the evaluation of cardiovascular risk for future diabetes drug applications.

After those discussions we are going to ask the committee to vote on the following question, which is identical for Saxagliptin and Liraglutide and it reads as follows. Based on the preceding discussion, has the applicant provided evidence of cardiovascular safety to conclude that Saxagliptin (today)/Liraglutide (tomorrow) rules out unacceptable excess cardiovascular risk relative to comparators, including evidence

that the upper bound of the two-sided 95% confidence interval for the risk ratios, odds ratios is less than 1.8.

This question is getting at two issues; one is this number of 1.8, and the second issue is the data that was used to generate the number that is being compared to 1.8. If the committee votes "No" to this question, what additional cardiovascular data are needed to address any limitations resulting from the completed clinical development program and to support approvability including satisfying the 1.8 non-inferiority margin.

Saxagliptin is going to have a second question; this question will not be asked of Liraglutide because it's not applicable there. The second question that the panel would be asked to vote on today reads as follows. For the custom MACE endpoint the upper bound of the two-sided 95% confidence interval for the risk ratios, odds ratio was less that 1.3. These data involved the total of 11 cardiovascular events in the 24-week double blind short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study periods of median 62 week exposure. Are these data adequate to conclude that post-marketing cardiovascular safety trials are unnecessary? If voting "No", please comment on the limitations of the completed NDA program that will require additional post-marketing trials.

In conclusion, the Saxagliptin and Liraglutide programs were completed prior to the diabetes cardiovascular guidance. These programs were not prospectively designed to measure cardiovascular risk. Nonetheless, FDA requests that these programs provide adequate evidence of cardiovascular safety to support marketing. Today we will hear the data from the applicant and FDA in this regard and we look forward to a thoughtful discussion from the panel. Thanks for your attention.

DR. BURMAN: Thank you very much. Thank you very much, Dr. Joffe. We will now proceed with the Sponsor presentations. I would like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel. I believe Dr. Lamendola is the first speaker.

SPONSOR PRESENTATION

BRISTOL-MYERS SQUIBB

INTRODUCTION

JOSEPH LAMENDOLA, PH.D.

Mr. Chairman, Members of the Endocrine and Metabolic Drugs Advisory Committee and FDA, good morning. My name is Joe Lamendola and I'm Vice President of Global Regulatory Sciences for Bristol-Myers Squibb.

In January of 2007 Bristol-Myers Squibb and AstraZeneca formed an alliance to develop novel therapies for the treatment of type 2 diabetes. Today we will present the results of our development program for Saxagliptin, a highly potent, selective and reversible DPP-4 inhibitor. We are seeking an indication for Saxagliptin to improve glycemic control in patients with type 2 diabetes, as an adjunct to diet and exercise, when used as monotherapy, combination therapy with Metformin, a TZD, or a Sulfonylurea, and as initial combination therapy with Metformin. A robust clinical development program was conducted where a total of 5,346 subjects were evaluated in phases 1 through 3. Treatment with Saxagliptin resulted in consistent clinically meaningful and statistically significant reductions in HbA1c, fasting plasma glucose, and postprandial plasma glucose.

We will also present safety results that show that Saxagliptin was well tolerated with a favorable adverse event profile. In addition, given the importance of demonstrating CV safety, we applied the principles outlined in FDA's recently issued guidance to assess the CV safety of Saxagliptin. The results of these comprehensive analyses indicate that there is no increased CV risk associated with Saxagliptin treatment. We conclude that Saxagliptin provides clinically meaningful glycemic benefits, is well tolerated with no evidence of an increase in CV risk, and provides a favorable benefit risk profile.

To present our results in more detail, I would like to introduce Dr. Robert Wolf, Vice President and Development Lead for the program, who will briefly describe an overview of the clinical and non-clinical development program.

Dr. Roland Chen, Group Director of CV Metabolics, who will then review the clinical pharmacology, efficacy, and safety of Saxagliptin. He will also show how we met or exceeded FDA's exposure guidelines for new therapies of type 2 diabetes.

As cardiovascular safety of therapies for type 2 diabetes has been the subject of intense interest and scrutiny, Dr. Wolf will then address the issue separately from other aspects of the profile of Saxagliptin and will provide an overall assessment of the benefit risk of the program.

Dr. Brian Daniels, Senior Vice President for Global Development and Medical Affairs, will then describe our commitment to continue to assess the benefit risk characteristics of Saxagliptin in the post-approval setting.

We are also very pleased to have with us today Dr. John Alexander, who is the Associate Professor of Medicine, Division of Cardiovascular Medicine at the Duke University Medical Center.

Dr. Mark Gorrell, who is Associate Professor at the Centenary Institute of Cancer Medicine in Cell Biology at the University of Sydney.

Dr. Princy Kumar, who is Professor Of Medicine and Microbiology and Chief of the Division of Infectious Diseases at Georgetown University School of Medicine.

Dr. Brian Strom, who is Professor of Public Health and Preventive Medicine and Biostatistics and Epidemiology at the University of Pennsylvania School of Medicine.

These individuals will also be available to address specific questions that you may have within their respective areas of expertise. I would now like to ask Dr. Wolf to come forward and to present an overview of our development program. Dr. Wolf.

OVERVIEW OF DEVELOPMENT PROGRAM

ROBERT WOLF, M.D., F.A.C.C.

Good morning. Prior to describing our development program, I'll provide a perspective on why it is important to develop novel therapies for type 2 diabetes. Although several agents are available to treat the hyperglycemia type 2 diabetes, many, if not most, patients fail to achieve the ADA recommended target of A1c less than 7.0%.

As shown in this slide, data from recent surveys indicate the majority of patients with type 2 diabetes in the US, the UK, and in Europe have A1c values above 7.0. Some of the currently available agents have tolerability or safety concerns including GI intolerability, risk for hypoglycemia, weight gain, and concerns regarding cardiovascular safety.

Type 2 diabetes is a progressive disease characterized by an increase in A1c over time, most likely due to progressive failure of the pancreatic beta cell. Thus, patients with type 2 diabetes who are well controlled today are likely to need new therapies in the future to maintain glycemic control. Unfortunately, type 2 diabetes is becoming more prevalent in younger age groups. This will likely increase the need for new therapies as younger patients face more years of progressive decline of beta cell function.

In summary, there are substantial unmet medical needs to provide new therapies for type 2 diabetes; particularly new therapies that provide safety and tolerability advantages over existing agents. The hyperglycemia type 2 diabetes is a consequence of both resistance to the biologic effects of Insulin and a deficit in production of Insulin in sufficient quantities to overcome this Insulin resistance. Nearly, all of the available therapies for type 2 diabetes address one or both of these pathophysiologic mechanisms. As we will see, Saxagliptin addresses both the deficit in Insulin protection by pancreatic beta cell and over-production of glucose by the liver, by modulating production of glucagon by the pancreatic alpha cell. An understanding of the incretin effect is essential to understanding the mechanisms of action for Saxagliptin.

A series of studies by other investigators have demonstrated an important difference in the Insulin response to an oral glucose challenge versus an intravenous glucose challenge. For a given level of plasma glucose the Insulin response is approximately 70% higher for oral versus intravenous administration of glucose. This is known as the incretin effect. This observation led to the discovery of small peptides that are secreted by neuroendocrine cells in the intestine. The two major incretin peptides, Glucagon-like peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide

(GIP) are both secreted in response to feeding and are largely responsible for the incretin effect in humans. Both peptides are inactivated by dipeptidyl-peptidase 4 (DPP-4).

The next slide summarizes how inhibition of DPP-4 can improve glycemia control in type 2 diabetes. Ingestion of food stimulates production of incretin peptides by neuroendocrine cells in the intestine. The incretin peptides GLP-1 and GIP are rapidly cleaved and inactivated by DPP-4. Inhibition of DPP-4 increases postprandial levels of GLP-1 by approximately two- to threefold. This postprandial increase in GLP-1 mediates an increase in Insulin secretion by the pancreatic beta cell and also mediates a decrease in glucagon secretion by the pancreatic alpha cell in a glucose dependent fashion. The net effect is the reduced blood glucose. As Dr. Chen will describe, Saxagliptin significantly reduces both postprandial and fasting levels of glucose. Some of the properties of Saxagliptin are described on the next slide.

Saxagliptin is a potent competitive inhibitor of DPP-4 with two orders of magnitude, or greater, selectivity for DPP-4 versus other proteases. It has an active, monohydroxy metabolite that is a twofold less potent inhibitor of DPP-4 than Saxagliptin. It is present in fourfold greater exposure and therefore contributes to in vivo DPP-4 inhibition activity.

The pharmacodynamic properties of Saxagliptin are consistent with once daily administration when given as a 5 mg dose. It is rapidly and extensively absorbed after oral administration, can be taken without regard to meals, and has predictable dose proportional pharmacokinetic behavior. Clearance of Saxagliptin and its active metabolite occur via metabolism in renal and non-renal routes of elimination.

I will now provide a brief summary of our non-clinical and clinical development programs. The non-clinical development program included in vitro and in vivo assessments of the pharmacodynamic, safety pharmacology and pharmacokinetic properties of Saxagliptin. We conducted multiple experimental studies of the metabolism of Saxagliptin and characterized the toxicology and toxicokinetics of Saxagliptin in multiple species.

We conducted an extensive clinical pharmacology program to characterize the safety, pharmacokinetics, and mechanism of action. We characterized the potential of drug-drug interactions, and studied Saxagliptin on multiple special populations. We initially characterized the safety and efficacy of Saxagliptin across a wide range of doses in a phase 2/b dose ranging study.

Our phase 3 registrational program informs the safety and efficacy of Saxagliptin in a wide range of patients. We designed our phase 3 program in consultation with the FDA. The program was designed to support an indication to improve glycemic control in adults with type 2 diabetes. The pivotal phase 3 studies inform the use of Saxagliptin as monotherapy, add-on combination therapy, and initial combination therapy.

Dr. Roland Chen will now provide a summary of the clinical profile of Saxagliptin. Dr. Chen.

CLINICAL EFFICACY AND CLINICAL SAFETY

ROLAND CHEN, M.D.

Thank you, Bob. The Saxagliptin Clinical Development Program was comprehensive and extensive. We studied over 5,300 subjects, of which more than 4,600 received Saxagliptin. A distinguishing feature of the clinical program was the evaluation

of a wide range of Saxagliptin doses from 1 to 400 mgs once daily. This enabled robust conclusions regarding dose selection as well as safety experience at doses in great excess of our proposed usual clinical dose. The program included over 670 subjects in clinical pharmacology studies, 423 patients in a phase 2b dose ranging study and over 4,200 patients with type 2 diabetes in phase 3 clinical trials.

In the clinical pharmacology program Saxagliptin given once daily was generally safe and well tolerated at doses up to 400 mgs for two weeks. That is 80x the proposed usual clinical dose of 5 mgs. There were no signals for QT prolongation or heart rate changes seen in a thorough QTC study. We observed no safety signals for hypoglycemia, localized edema or skin lesions. In addition, we saw no hepatics, striated muscle, and renal safety signals in laboratory blood tests.

We observed no clinically meaningful pharmacokinetic differences in adult sub populations as assessed by less than twofold differences in the sum of Saxagliptin and active metabolite exposures including by age, gender, weight, hepatic impairment or mild renal impairment. Higher Saxagliptin and active metabolite exposures were noted in patients with moderate or severe renal impairment and end stage renal disease. These patients will be managed with a dose adjustment to one half of the usual clinical dose, that is, to 2.5 mgs once daily.

In a series of drug-drug interaction studies we found low potential for pharmacokinetic drug-drug interactions with a number of commonly used oral antidiabetic agents as well as other agents commonly used in this patient population including a Statin, gastric acid controllers, and Digoxin. Drug-drug interactions with strong CYP3A inhibitors or induces are minimized because changes in parent drug exposures were offset by opposite changes in active metabolite exposures.

The Saxagliptin phase 2b/3 clinical program consisted of eight studies. These studies included over 4,600 patients of which more than 3,400 received Saxagliptin. The program included a phase 2b monotherapy dose ranging study, six pivotal phase 3 studies and a phase 3 mechanism of action study. The six pivotal studies evaluated Saxagliptin over a range of different treatment modalities including administration as monotherapy, add-on combination treatment, and as initial combination therapy with Metformin.

Saxagliptin was evaluated in a phase 2b dose ranging study that included 423 patients. This was a randomized controlled study that included five Saxagliptin doses of 2.5 mgs, 5 mgs, 10 mgs, 20 mgs and 40 mgs compared with placebo given for 12 weeks. The study demonstrated greater lowering of A1c and fasting glucose at the 5 mg dose compared with the 2.5 mgs dose without evidence for incremental benefit at higher doses. There was no dose limiting toxicity observed in this study. As a consequence, doses of 2.5 mgs, 5 mgs and 10 mgs once daily were chosen for further study in the phase 3 program. 5 mgs were included in all studies in the phase 3 program. 2.5 mgs enabled further study at the lower end of the dose range, and 10 mgs provided additional safety experience at the high end of the dose range and addressed whether greater efficacy would be evident with longer exposure beyond 12 weeks.

The pivotal phase 3 studies enroll patients with inadequate glycemic control across a range of A1c values by study. Age of the entry was 18 to 77 years. Patients were excluded who had a recent significant cardiovascular event. In addition, patients were excluded who had history of significant heart failure. Patients were also excluded if they were immunocompromised. For example, having undergone organ

transplant or diagnosed with HIV, or demonstrated abnormalities on screening tests with hepatic, renal or hematologic function.

The six pivotal phase 3 studies were randomized, double blind, control parallel arm and multi-center in design. All studies had a placebo lead-in period followed by a 24-week double blind short-term period. These studies included controlled extensions of 12 to 42 months, allowing long-term comparisons of Saxagliptin relative to control therapies. In order to allow patients with worsening glycemic control to remain safely in the studies, there was provision for rescue medication based on pre-specified glycemic criteria. These studies shared a common primary endpoint and a number of key secondary endpoints.

The primary endpoint was change in A1c from baseline to week 24 of double-blind treatment, secondary endpoints included change from baseline to week 24 in fasting plasma glucose, proportionate patients achieving a therapeutic glycemic response to find his A1c of less than 7% at week 24, and change from baseline to week 24 in the area under the curve from zero to 180 minutes for postprandial glucose response to a standard oral glucose challenge. All efficacy endpoints were evaluated prior to the initiation of rescue therapy.

Two of our six phase 3 studies examine Saxagliptin given as monotherapy in treatment-naive patients with A1c values ranging from 7% to 10% at baseline. The first study randomized approximately 400 patients to Saxagliptin given at fixed doses of 2.5 mgs, 5mgs, or 10 mgs versus placebo. In this study Saxagliptin led to decreases of 0.43%, 0.46% and 0.54% from baseline. The decreases in A1c were statistically significant versus placebo for all three treatment groups.

The second study, which was smaller in size, randomized 365 patients to one of five treatment arms, Saxagliptin 2.5 mgs or 5 mgs given once in the morning, Saxagliptin 2.5 mgs with provision for titration to 5 mgs based on pre-specified glycemic criteria, Saxagliptin 5 mgs given in the evening, or placebo. In this study Saxagliptin led the decreases in A1c from baseline ranging from 0.61% to 0.71% as was the case for the first monotherapy study the decreases in A1c were statistically significant versus placebo for all treatment groups.

Type 2 diabetes is a progressive disease and many patients require combination treatment to achieve adequate glycemic control. As such, we performed three studies of Saxagliptin given as add-on therapy to patients inadequately controlled on three commonly used classes of medication. In the first study, 743 patients inadequately controlled on 1,500 mgs or greater of Metformin were randomized to Saxagliptin 2.5 mgs, 5 mgs, or 10 mgs versus placebo in addition to their previous Metformin dose. In this study Saxagliptin led to decreases in A1c of 0.59%, 0.69% and 0.58% from baseline, decreases that were all statistically significant versus placebo.

In the second study, 565 patients inadequately controlled on either 30 mgs or 45 mgs of pioglitazone or 4 mgs or 8 mgs total daily dose of rosiglitazone were randomized to Saxagliptin 2.5 mgs or 5 mgs versus placebo, in addition to their TZD regimen upon study entry.

In this study, Saxagliptin led to reductions in A1c of 0.66% and 0.94% from baseline. These changes were also statistically significant compared to placebo. In the third study a total of 768 patients inadequately controlled on a sub maximal dose of Sulfonylurea were all placed on a standard dose of 7.5 mgs glyburide upon entering a

four-week placebo lead-in period. The patients were then randomized to Saxagliptin 2.5 or 5 mgs added on to 7.5 mgs glyburide versus 10 mgs of glyburide.

In the glyburide monotherapy arm, titration of glyburide was permitted in blinded fashion to 15 mgs in the short-term period. Approximately 92% of patients in this group received 15 mgs at the end of the study period. This was thus a study of Saxagliptin added on to a mid-dose SU versus continued up titration of the mid-dose monotherapy SU. There was little effect observed in the up titrated glyburide arm as compared to decreases in A1c of 0.54% and 0.64% in the Saxagliptin 2.5 mgs and 5 mgs arms. These changes were both statistically significant versus control. Of note, in all three studies the 5 mgs group led to the greatest numerical decrease in A1c.

Initial anti hyperglycemic monotherapy is frequently insufficient to enable patients with type 2 diabetes to reach glycemic targets. We conducted a study that assessed the safety and efficacy of Saxagliptin plus Metformin given as initial therapy versus Saxagliptin or Metformin monotherapy in treatment naive patients with higher A1c values at baseline. That is, a patient population less likely to reach goal on monotherapy alone.

In this study eligible patients were randomized to one of four treatment groups; Metformin monotherapy, Saxagliptin monotherapy at 10 mgs once daily, Saxagliptin 5 mgs once daily plus Metformin, and Saxagliptin 10 mgs once daily plus Metformin. In the three treatment groups that contain Metformin, Metformin could be titrated to achieve a maximal total daily dose of 2,000 mgs. Saxagliptin 5 or 10 mgs given as initial combination treatment led to similar decreases in A1c of 2.5%. These changes were statistically significant compared with both monotherapy components alone. In the studies just presented as described in our briefing book, the proportion of

patients who achieve the pre specified glycemic goal of A1c less than 7% was also larger in the Saxagliptin treatment groups compared with the control groups.

The study of multiple doses in the phase 2b/3 program enhanced our ability to further understand the dose response for efficacy. This figure summarizes A1c lowering for the 2.5 mg and 5 mg groups over four treatment paradigms, that is, as monotherapy, add-on treatment to Metformin, add-on to TZD, and add-on to SU, based on findings from the six phase 2b/3 studies that contain this dose. In order to further understand the effects of Saxagliptin as monotherapy, we performed post-hoc pooled analysis of the three phase 2b/3 monotherapy studies for A1c lowering at week 12. The monotherapy studies were the smallest in our clinical program. This analysis enabled us to incorporate the entirety of our monotherapy experience at a common time point.

In all four treatment paradigms the 5 mgs group provided greater efficacy than the 2.5 mg group. The difference in A1c lowering was 0.1% to 0.3% greater for the 5 mg versus 2.5 mg group. The aggregate data support the 5 mg dose as the usual clinical dose. Overall, in all treatment paradigms that is, Saxagliptin given as monotherapy or as add-on treatment to Metformin, TZD, or SU, A consistent efficacy benefit was observed for Saxagliptin 5 mgs versus 2.5 mgs. These results are consistent with observations of greater DPP-4 inhibition at trough with the 5 mg versus 2.5 mg dose.

In contrast, there was no evidence for an incremental efficacy benefit for 10 mgs versus 5 mgs. As we will show later, the safety profile with the 2.5 mg and 5 mg groups were generally comparable. As a consequence, 5 mgs is our proposed usual clinical dose. The preceding analyses have focused on changes from baseline in A1c, the 5 mg dose also proved to be effective when we assessed its impact on postprandial glucose and fasting plasma glucose. We observed clinically meaningful and statistically

significant decreases in glucose at 120 minutes as well as three-hour glucose area under the curve following standard oral glucose challenge versus control.

As shown in this figure, in the six pivotal phase 3 studies, Saxagliptin 5 mgs led to decreases of 31 mgs to 50 mg/dL relative to control in two-hour plasma glucose. The reductions in postprandial glucose we saw in conjunction with increases in Insulin provide evidence for the effect of Saxagliptin in improving beta cell function.

In addition, we also observed decreases in postprandial glucagon during this period, supporting a beneficial effect at the level of the alpha cell. In addition to decreasing plasma glucose following oral glucose challenge, treatment with Saxagliptin led to statistically significant reductions in fasting plasma glucose versus control in all phase 3 studies. In the six pivotal studies, Saxagliptin 5 mgs led to decreases in fasting plasma glucose ranging from 10mgs to 23 mg/dL relative to control. In these studies, differences in fasting plasma glucose between Saxagliptin and control were seen as early as week two, the earliest time point of measurement. The impact of Saxagliptin on fasting plasma glucose provided clinical evidence for improvement in basal beta cell function as also indicated by corresponding increases in phase 2b.

Treatment with Saxagliptin consistently led to beneficial antihyperglycemic effects across subgroups of demographic and baseline diabetes characteristics. This figure summarizes control subtracted A1c lowering from baseline by gender, race, age, A1c at baseline, duration of diabetes, and creatinine clearance for Saxagliptin 5 mgs as add-on therapy to Metformin. Consistent and clinically meaningful reductions in A1c that is between 0.6% and 1% were seen for all sub groups.

In summary, Saxagliptin 5 mgs given as monotherapy, add-on combination treatment, and initial combination therapy with Metformin led to consistent,

clinically meaningful, and statistically significant reductions in A1c, fasting plasma glucose, and postprandial glucose, together with increases in achievement of treatment targets. In addition, Saxagliptin led to beneficial effects across various sub groups of demographics and baseline diabetes characteristics.

Saxagliptin safety profile was studied across a wide range of doses in the clinical development program. Our development program provided clinical experience at high multiples of our proposed usual clinical dose of 5 mgs. This included exposures of 400 mgs. That is 80 x the proposed 5 mg dose, for two weeks, 100 mgs for six weeks, 40 mgs and 20 mgs for 12 weeks, and 10 mgs for 102 weeks. Three doses of Saxagliptin were evaluated in the phase 3 program with approximately one-third of the experience accrued at 10 mgs or two times that of the proposed usual clinical dose. Saxagliptin was well tolerated at all doses without any dose limiting toxicity. The numbers of patients included in the Saxagliptin phase 2b/3 program either met or exceeded guidelines issued by both ICH and FDA as shown in this table.

In 1995, ICH issued guidance on exposure to assess clinical safety for drugs intended for the long-term treatment of non-life threatening conditions. In February of 2008, the FDA issued a new draft guidance for the development of drugs for treatment of type 2 diabetes. In this guidance, the FDA identified target numbers for patients exposed to the investigational agent for one year and for 18 months. As shown in this table we either met or exceeded both guidances at the time we filed the NDA for Saxagliptin. By the time we filed the day 120 update to the FDA we had accrued substantial additional long-term experience. By that time more than 2,000 patients were exposed for one year, 1,000 for 18 months, and 400 for two years. In addition, we

worked with FDA to ensure that the development program provided adequate exposure for each of the intended Saxagliptin indications.

The safety of Saxagliptin was evaluated through standard adverse event and laboratory parameter review. These measures were complemented by a program to collect supplemental data for events of special interests. Events were identified as being of special interest based on findings observed in the Saxagliptin non-clinical program, in the phase 1 and 2b programs at higher doses, safety related concerns reported for other DPP-4 inhibitors, and theoretical considerations related to the mechanism of action of DPP-4 inhibitors. Monitoring activities included ongoing identification of events and use of supplemental case report forms to gather additional information on the following types of events; skin lesions, selected infections, decreased lymphocytes or platelet counts, and localized edema.

At the start of the phase 3 clinical development program we established an independent data monitoring committee. The DMC periodically reviewed the accumulating Saxagliptin safety data from the six pivotal phase 3 studies. The DMC has allowed all studies under its review to continue at all doses and has not required any study modifications. The Saxagliptin safety database was studied using complementary populations, analyzed at different time points to enhance detection of potential safety signals. Study level analyses enabled evaluation of Saxagliptin administered under different treatment conditions. The placebo controlled pool population allowed for integrated analysis of small numerical imbalances seen within the five placebo controlled pivotal phase 3 studies.

The phase 2b/3 pool population incorporated the controlled experience of all eight phase 2b/3 studies enabling comprehensive evaluation of relatively infrequent

events including deaths, certain AEs, and infrequent laboratory abnormalities. We conducted analysis for the following study periods: the short-term, 24-week period, excluding rescue therapy in order to avoid confounding a rescue treatment. Short-term 24-week periods including rescue therapy in order to address imbalances and exposure to blinded study medication across treatment groups. The short-term plus long-term periods to provide the most complete longitudinal experience. This is particularly valuable for the evaluation of infrequent events and to understand effects with long-term repeated dosing

The phase 2b/3 program included a range of patients with type 2 diabetes. The mean age across these studies was approximately 54 years with about 15% above 65 years. The majority of patients were White, comprising approximately 70% of the population. There was a fairly even distribution of male and female patients. The mean duration of diabetes ranged from 3.6 to about five years across the treatment groups. This variation was reflective of the 10 mgs dose only being included in some of the phase 3 studies.

As expected, mean duration of diabetes was shorter in the monotherapy and initial combination studies where treatment naive patients were enrolled. Patients in the add-on combination studies had longer mean duration of diabetes. Patients entered with a broad range of A1c values reflecting varying degrees of glycemic control by study. Approximately 17% of patients had mild renal impairment as estimated using the Cockroft-Gault formula. Approximately 16% to 17% of patients had a history of microvascular complications upon study entry.

The remainder of the safety presentation will provide an overview of the following topics: overall adverse events, serious AEs, and discontinuations for AEs,

hypoglycemia, dermatologic safety, lymphocytes, and an overall summary of the general safety profile. Additional details of the Saxagliptin safety profile can be found in our briefing book. Our safety review will primarily focus on the cardiovascular profile with Saxagliptin, our initial assessments of CV safety reflected the concern with cardiovascular disease as the leading cause of morbidity and mortality in patients with type 2 diabetes. In addition, a comprehensive set of analyses were undertaken in light of recent final guidance from FDA on evaluating CV risk and will be presented later by Dr. Wolf.

Dr. Wolf will also further describe the cardiovascular history and risk factors of this population. Saxagliptin was well tolerated with monotherapy and in combination with other oral antihyperglycemic agents. This table provides a summary of adverse events based on an analysis of the placebo controlled pool population up to week 24 including rescue therapy. The frequency of patients with adverse events treated with Saxagliptin 5 mgs was similar to placebo. 72.2% compared with 70.6%. There was no discernible difference in the clinical AE profile between the Saxagliptin 2.5 mgs and 5mg groups. Deaths and serious adverse events were infrequent and occurred at comparable frequencies between patients who received Saxagliptin and placebo.

We also observed similar findings across treatment groups in our initial combination study with Metformin. AEs leading to discontinuation from study therapy were infrequent in all treatment groups and were reported in 2.2%, 3.3%, 3.9% and 1.8% of patients in the Saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In contrast, as described in the briefing book, in the initial combination therapy study with Metformin, AEs leading to discontinuation were similar in each of the treatment groups, which contain Saxagliptin and in the Metformin monotherapy group.

DPP-4 inhibitors augment the action of GLP-1, increasing Insulin secretion in a glucose dependent manner thereby minimizing the risk of hypoglycemia. This table summarizes both reported and confirmed events of hypoglycemia for Saxagliptin in the phase 3 studies and for the placebo controlled pool population. In accordance with its mechanism of action, the frequency of reported hypoglycemia, that is symptoms of hypoglycemia, in patients who received Saxagliptin 5mgs as monotherapy or in combination with Metformin or TZD was similar to those reported in patients who received placebo.

The incidence of hypoglycemia was numerically higher for patients who received Saxagliptin 5 mgs added to an intermediate dose of SU compared with up titration of SU monotherapy. The difference, 14.6% compared with 10.1%, was not statistically significant. Events of confirmed hypoglycemia, defined as symptoms of hypoglycemia and with fingerstick blood glucose measurement less than or equal to 50 mg/dL, were infrequent and also occurred at similar rates for Saxagliptin 5 mgs and placebo under all treatment conditions.

Similarly, in our initial combination study with Metformin, the incidence of reported hypoglycemia in patients who receive Saxagliptin in combination with Metformin, whereas monotherapy at 10 mgs range from 1.5% to 5%, compared with 4% in those patients who received Metformin monotherapy.

In non-clinical studies, we observe multi-focal reversible skin lesions (erosions and ulcers), in cynomolgus monkeys exposed to Saxagliptin. As a consequence, we closely monitored skin related adverse events in the phase 3 program, including measures to provide investigator training and supplemental data collection

using special case report forms. We developed a pre-specified list of MedDRA preferred terms intended to be potentially correlative to the non-clinical monkey findings.

The list, which was reflective of ulcerative and necrotic skin conditions, was used to identify events of interest in the phase 3 program for further evaluation. We observed that these events were infrequent without imbalance between Saxagliptin in control and did not lead to study drug discontinuation. None was considered related to study drug as assessed by the investigators. Typically the events appear to be secondary to underlying disease or external factors, such as trauma. Overall, the evaluation of clinical data has not revealed signals that correlate to the non-clinical monkey skin findings.

In the Saxagliptin development program we noted decreases in lymphocyte count in phase 1 and 2b studies of Saxagliptin at higher doses. As the consequence, we monitored lymphocyte counts carefully in the phase 3 program. In phase 3 we saw a small dose dependent reduction in mean absolute lymphocyte count at the 5 mg and 10 mg dose. The decreases were on the order of approximately 100 cells per mL relative to placebo from a mean baseline lymphocyte count of approximately 2,200 cells per mL. The decreases were non-progressive with daily dosing of Saxagliptin to 128 weeks. These lymphocyte count decreases were not associated with clinically adverse consequences.

In patients with low lymphocyte counts, the types of infections we observe were similar to those seen in the general population. That is, without unusual opportunistic infections. Further, the frequencies of infection related AEs were comparable for the Saxagliptin 5 mg and placebo doses without signal for opportunistic events in the overall population.

Overall, Saxagliptin was well tolerated at all doses studied in the phase 3 program. There was low risk for hypoglycemia. As described in the briefing book, we observed no adverse effects with respect to lipid parameters, blood pressure, or heart rate. Saxagliptin was associated with no or minimal differences in weight change compared with control. In addition, we identified no hepatic, pancreatic, skeletal, myopathy, or renal safety signals and there was no evidence for clinically meaningful or consequential effects on laboratory parameters.

With this, I would like to introduce Dr. Wolf, who will review the Saxagliptin cardiovascular safety profile. Thank you.

CARDIOVASCULAR SAFETY PHARMACOVIGILENCE PLAN

BENEFIT-RISK

ROBERT WOLF, M.D., F.A.C.C.

Thank you, Roland. While the cardiovascular safety profile of treatments for type 2 diabetes has always been of interest, the regulatory environment for this topic evolved prior to and after we filed the NDA for Saxagliptin.

This slide summarizes how we adapted to this changing environment and collaborated with the FDA to generate the data needed to assess the cardiovascular safety profile for Saxagliptin. The FDA has outlined key design features for clinical development programs to ensure adequate assessment of CV safety. The details are discussed in the Agency's guidance document in our briefing book. The FDAs criteria for assessing CV safety of new therapies are summarized in the next slide.

As Dr. Joffe described, the FDA specified criterion to assess approvability of treatments for type 2 diabetes would indicate that the upper band for the confidence interval should be less than 1.8 in order for the product to be approvable. As described in

our overview, we analyzed acute CV events prior to submitting the NDA for Saxagliptin. We also retrospectively applied FDA guidance on evaluating CV risks to the clinical data for Saxagliptin by assessing multiple additional types of CV events utilizing multiple analytic methods.

The intent at using multiple types of CV events and multiple analytic methods was to assess the consistency of our results given the retrospective nature of many of our assessments. We use endpoints and methods defined by both us and by the agency. I would now like to provide some context for our assessment of CV safety in the phase 2b/phase 3 clinical programs.

In non-clinical studies performed on multiple species, we did not see microscopic evidence of cardiotoxicity and did not see evidence of adverse electrophysiologic or hemodynamic effects of Saxagliptin. In our phase 1 clinical program, we studied Saxagliptin at doses up to 80x the proposed usual clinical dose. We did not see an adverse effect on lipid parameters, blood pressure, heart rate, or QT interval. For another member of the DPP-4 class, currently approved for clinical use in the United States, published data indicated no meaningful differences in the incidence rates for cardiac related or ischemia related adverse experiences. Thus the data available to us prior to our analyses of the phase 2b, phase 3 clinical program did not suggest that CV risk would be associated with Saxagliptin.

I will now provide an overview of the methods used to analyze CV events in the Saxagliptin clinical program. While we analyze CV events defined by us and by the Agency it is important to know if the analyses of these events were based upon a common database and common analytic methods. For all pooled analyses we use

randomized control data from approximately 4,600 patients enrolled in phase 2b and phase 3 studies. Approximately 3,300 of these patients were exposed to Saxagliptin.

The FDA requested analyses of both the short-term and a short-term plus long-term experience in our program. I will present data from the short-term plus long-term phase of our studies assessed until the time of the day 120 safety update, as this provides the most comprehensive longitudinal description of CV events in our program. This experience reflects 5,000 patient-years of exposure including 3,700 patient-years of exposure on Saxagliptin. All pooled analyses of CV events were stratified by study in recognition of the fact that CV risk profile may have varied across individual trials.

The FDA requested that we calculate risk ratios for CV events based on the incidence rate ratio and the incidence ratio. The FDA permitted us to use other methods of analyses, so we also calculated hazard ratios based on the Cox proportional hazard regression method. These methods were consistently applied to our pooled assessment of risk ratio. For the sake of simplicity, I will initially focus on the four major CV endpoints that were analyzed. These endpoints are listed on this slide in the approximate order in which we analyzed them. Identification of CV endpoints was primarily based upon searching our adverse event database for events that coded to particular preferred terms in the MedDRA dictionary as described by Dr. Joffe.

The number of preferred terms used to identify each endpoint is listed in the middle column. While the number of patients identified with each endpoint is listed in the last column highlighted in light blue. Our initial assessment of CV safety initiated prior to submission of the NDA was based upon the endpoint acute cardiovascular events. This endpoint targeted CV events that were acute, ischemic and consequential. It was a

relatively broad endpoint that included both reversible and irreversible ischemic events. It also included revascularization procedures.

Cases of acute CV events were identified in the adverse event database based on searching for 117 preferred terms in the MedDRA dictionary. We identified 61 patients with acute CV events. Subsequent to submitting the NDA, we analyzed MACE (Major Adverse Cardiovascular Events). MACE was a composite endpoint that encompassed CV death, nonfatal myocardial infarction, and nonfatal stroke. Three definitions of MACE were initially investigated. For each type of MACE, case identification was based upon searching the adverse event database using specific lists of preferred terms supplemented by clinical review of all deaths to ensure that each death with a CV etiology was counted.

As can be seen in this slide, the three types of MACE varied in the breadth of preferred terms that were used for case identification. Primary MACE defined by us and custom MACE defined by the Agency had the shortest list of preferred terms consisting of 54 and 33 terms, respectively. We identified 41 patients with primary MACE and 40 patients with custom MACE. In contrast, SMQ MACE defined by the FDA was based upon a list of 148 preferred terms. As expected, this more broadly defined endpoint identified a larger number of patients; that is, 141 patients. The relationship of these four endpoints is important for the interpretation of the results.

On the next slide I'll explain the relationship of patients with these endpoints using a series of Venn diagrams. The relationship with the two most broadly defined endpoints, SMQ MACE and acute CV events, is described at the top of the slide. There were 141 patients with SMQ MACE and 61 patients with acute CV events. There were 46 patients in the overlap; that is, patients whose events were classified as both

SMQ MACE and acute CV events. However, there were clear differences in these two populations as shown. Among the patients with SMQ MACE but not acute CV events, a majority were accounted for by the single preferred term, a blood creatine phosphokinase increase, which was in the FDAs definition of SMQ MACE.

The relationship of the two most narrowly defined endpoints, custom MACE and primary MACE, is shown at the bottom of the slide. There were 40 patients with custom MACE and 41 patients with primary MACE. There were 40 patients in the overlap. In other words, custom MACE and primary MACE identified nearly identical sets of patients differing by a single individual. This is important because the results for primary MACE will be nearly identical to the results for custom MACE.

Next I will summarize the results of our analysis of CV events. I will begin by describing the CV risk profile in the phase 2b/phase 3 pool population. The presence of type 2 diabetes in and of itself is a significant risk factor for future CV events as noted in various epidemiologic studies. 80% of the patients in our pool phase 2b/phase 3 population had at least one of the four additional risk factors for cardiovascular events that are listed on this slide.

There are 569 patients in our experience who had clinically evident cardiovascular disease upon entry to the phase 2b/phase 3 studies defined as a prior history of myocardial infarction, heart failure, angina pectoris, coronary, carotid or peripheral vascular disease or prior revascularization procedures.

Dr. Chen previously described the prevalence of some other potential risk factors including male gender and duration of type 2 diabetes. Our statistical analysis plan specified primary MACE as the primary endpoint for assessment of the cardiovascular safety profile for Saxagliptin. Accordingly, the next few slides will focus

on the results of a primary MACE. However, as stated previously, the results for the FDA defined endpoint of custom MACE would be nearly identical to the results for primary MACE.

This slide depicts the time to onset of first primary MACE using a weighted Kaplan Meier estimate for cumulative proportion. The X-axis represents time measured in weeks, the Y-axis represents the cumulative percent of patients with primary MACE. The data in this figure do not indicate increased risk for primary MACE for Saxagliptin treatment patients during either the short-term or the long-term phase of our studies.

The next slide summarizes the incidence rate ratio for primary MACE. The incidence rate ratio for primary MACE for the phase 2b/phase 3 pool population is shown at the top of the slide. The incidence rate ratio for each individual study is shown below. The point estimate and the 95% of confidence intervals are shown relative to a vertical line drawn at unity. Data to the left of the vertical line indicate the Saxagliptin is better, data to the right of the vertical line indicate the control is better.

In the pooled analysis the upper bound or the 95% confidence interval for the incidence rate ratio was 0.83. As expected, there was some variability in the point estimate for each individual trial, but there was considerable overlap in the confidence intervals indicating consistency in results for the trials in the phase 2b/phase 3 program. Our statistical analysis plan specified that we would analyze primary MACE in sub groups of patients with clinical evidence of cardiovascular disease and with cardiovascular risk factors.

Our analysis plan specified sub groups of patients who are believed to be at increased risk of CV events based on epidemiologic data. Those sub groups included

patients with clinically evident cardiovascular disease, and patient history had at least one or two additional risk factors for CV events, like a prior history of hypertension, hypercholesterolemia, smoking, or family history of premature coronary artery disease. The two most common of these risk factors, hypertension and hypercholesterolemia were analyzed separately as were male gender in age of at least 65 years.

The incidence rate for primary MACE in controlled patients, expressed in events for 1000 patient-years is shown in grey. The error bars represent the standard error to the mean. The incidence rate for primary MACE in Saxagliptin exposed patients is shown in yellow. Based on the incidence rate we do not see evidence for increased risk in sub groups, Saxagliptin exposed patients. The frequency of the four major CV endpoints in the pool population is summarized on the next slide. The frequency of major CV endpoints for Saxagliptin versus control highlighted in light blue do not indicate a signal for increased cardiovascular risk among Saxagliptin exposed patients. We also did not see evidence for dose response relationship for Saxagliptin doses at 2.5 mg to 10 mgs.

As described in our briefing document, several other CV endpoints were analyzed. The FDA requested that we analyze subsets of cardiac disorder adverse events corresponding to ischemic heart disease, cardiac failure, cardiac arrhythmias and a category of other events corresponding primarily to structural disorders like valvular heart disease. As can be seen in this slide, the data for these endpoints do not indicate a signal for increased CV risk among Saxagliptin exposed patients. We also analyzed the secondary MACE endpoint that counted all deaths not just those deaths attributed to cardiovascular etiology. Again, we did not see a signal for increased secondary MACE among Saxagliptin exposed patients.

I want to call your attention to the data for all-cause of death and CV death at the bottom of the slide. Consistent with our other analyses, we did not see evidence for increased risk of death among Saxagliptin exposed patients. The risk ratios for custom MACE and SMQ MACE are summarized on the next slide. When the results for all three analytic methods for custom MACE and SMQ MACE are depicted together, there is a consistent pattern for the upper bound with a 95% confidence interval for risk to be well within the FDA defined criterion for approvability.

The estimates of the risk ratio were lower for the more selected custom MACE than for the broad or inclusive SMQ MACE. Again, this difference between custom MACE and SMQ MACE is largely accounted for by including the term, 'blood creatine phosphokinase increase' in the FDA's definition for SMQ MACE. We do not see evidence of a cardiovascular safety signal for Saxagliptin based on these analyses. The risk ratios for primary MACE and acute CV events are summarized on the next slide.

The Cox hazard ratio, incidence rate ratio, and incidence ratio all gave consistent results for these Sponsor defined cardiovascular endpoints. The upper bound of the 95% confidence intervals for the risk ratio for the pool analyses were below 1.1 for both endpoints.

Again, well within the FDA criterion for approvability. We have asked Drs. John Alexander and Ken Mahaffey at the Duke Clinical Research Institute to perform a blinded review of the clinical data for all patients with SMQ MACE, primary MACE in all deaths. They review case report forms, narratives and source documents like discharge summaries and ECG's without knowledge of treatment group assignment. They independently identified 40 cases of MACE in this data set. The distribution of

these cases by treatment group was very similar to the distribution for primary MACE. Thus this external review was consistent with a lack of a CV safety signal for Saxagliptin.

The major importance of these analyses is to exclude a CV safety signal for Saxagliptin. It has not escaped our attention that a cardioprotective effect of Saxagliptin is possible. Given the limitations of the current data, a cardioprotective effect can only be hypothesized at this time. However, we are currently planning studies to rigorously test the hypothesis cardioprotection.

To summarize, we analyze multiple cardiovascular events using multiple analytic techniques to access the consistency of the results. We use methods developed by the FDA as well as our own methods for these analyses. We also employed blinded external review of MACE to confirm our results. We analyzed CV endpoints in the phase 2b/phase 3 pool population, in sub groups defined by increased risk for CV events, and in individual trials. While there are limitations to the retrospective applications of the FDA guidance to the Saxagliptin clinical database, the results of these analyses are consistent with the FDA criterion for excluding an unacceptable cardiovascular risk.

I would like to now provide some comments on the benefit risk profile for Saxagliptin and provide a rationale for approval of this product. There is epidemic growth in the prevalence of type 2 diabetes in the US and worldwide, many patients are not achieving treatment goals for glycemic control. Due to progression of this disease, monotherapy of type 2 diabetes often fails requiring most patients to require a combination therapy. Effective combinations often target complementary mechanisms of action to address the multiple metabolic defects of type 2 diabetes. There are safety and tolerability concerns for some existing agents.

In summary, there is substantial unmet need for new treatments of type 2 diabetes, particularly for new therapies that address some of the tolerability and safety issues associated with currently available agents. Saxagliptin provides clinically meaningful improvements in glycemic control as shown by consistent effects to reduce hemoglobin A1c, fasting plasma glucose and postprandial glucose. The glycemic benefit of Saxagliptin has been demonstrated when given as monotherapy, add-on combination therapy, and initial combination therapy.

This benefit is consistently seen across sub groups of patients. Saxagliptin effects improved beta cell function and alpha cell function are complementary to the mechanism of action for existing therapies, making Saxagliptin a good option as either monotherapy or as combination therapy. Saxagliptin has been studied on a large clinical development program at exposures up to 80x the proposed usual clinical dose, 5 mgs once daily.

It was well tolerated at all doses studied in phase 3, including a substantial experience at twice the proposed usual clinical dose. It has a low risk for hypoglycemia, has no or minimal differences in body weight change compared to control, and has no identified clinical signal for hepatic, pancreatic or renal safety concerns. There is no human clinical correlate to skin findings seen in monkeys. There was a small decrease in mean lymphocyte count that was not progressive and not associated with infectious related adverse outcomes.

Given concerns regarding the cardiovascular safety profile of new therapies for type 2 diabetes, we performed numerous meta-analyses of the long-term experience of Saxagliptin and eight randomized controlled phase 2b/phase 3 studies. These meta-analyses included data from over 3,300 patients exposed to Saxagliptin for

up to two and a half years. In these meta-analyses we did not see a cardiovascular safety signal for Saxagliptin. Thus, Saxagliptin provides meaningful benefits on glycemia control with a favorable safety profile. Compared with several of the available agents for type 2 diabetes, Saxagliptin provides an improved tolerability and safety profile with respect to hypoglycemia, weight gain, gastrointestinal adverse events, heart failure and edema. Saxagliptin offers a new treatment option with a favorable benefit risk profile for patients with type 2 diabetes.

Dr. Brian Daniels, Senior Vice President for Global Development and Medical Affairs at Bristol Myers-Squibb, will now describe our plan to continue to assess Saxagliptin if it is approved for clinical use in the United States.

ASSESSMENT OF SAXAGLIPTIN POST-APPROVAL

BRIAN DANIELS, M.D.

Thanks Bob. The positive benefit risk discussion Dr. Wolf just presented represents our current understanding in the profile of Saxagliptin. Both BMS and AstraZeneca are committed to the continued assessment of the benefit risk profile of Saxagliptin post-approval. The assessment of the post-approval profile of Saxagliptin will be achieved through three approaches; A comprehensive sweep of a post-marketing pharmacovigilance practices, the analysis of observational data, and the analysis of randomized clinical trial data.

Post marketing pharmacovigilance practices include the collection and evaluation of individual spontaneous safety reports and enhanced by the use of targeted questionnaires like those used during our phase 3 program. Also, there will be periodic assessments of the aggregate safety data compared with the FDA errors database for safety signal detection. A large pharmacoepidemiology program will use observational

data to identify and compare patients taking Saxagliptin with other oral antidiabetic agents on the market. These studies are planned using existing healthcare databases in both United States and the European Union. One of the outcomes under study will be major cardiovascular adverse events. Both of these programs are described in greater detail in your briefing book. These two complementary approaches, enhanced pharmacovigilance and observational studies, will allow for this continued assessment of the tolerability and safety of Saxagliptin throughout its life cycle.

Lastly, randomized clinical trail data would be generated through our program of 3b and 4 clinical settings, which will independently adjudicate cardiovascular events. These studies include the use of Saxagliptin with Insulin in several active comparator controlled studies.

Now, based on the clinical profile of Saxagliptin established to-date we are planning a randomized controlled event driven clinical trial. The objective of this trial is to characterize the long-term benefits of Saxagliptin in the management of type 2 diabetes. This study will further develop the cardiovascular profile of Saxagliptin using prospective adjudication and analysis of events in a population at an elevated risk. This is yet another mechanism for the continued assessment of the clinical profile of Saxagliptin post-approval.

In the cardiovascular metabolic disease areas both Sponsors Bristol-Myers Squibb and AstraZeneca have established a history of characterizing the long-term benefits for agents such as Pravastatin, Rosuvastatin and Clopidogrel. We plan to continue this legacy of post-approval assessment of benefit risk with Saxagliptin in this new area. We are excited about the possibilities that the contribution of Saxagliptin can

make in the care of patients with type 2 diabetes. We look forward to your discussions and thank you.

DR. BURMAN: Thank you very much. Because of technical difficulties if it is all right we are going to have our break now for 15 minutes and then come back and have questions for the Sponsor and then move on to the FDA discussion. We will try to resolve the technical issues. On the 15-minute break please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any other members, we will resume at 10:05.

(Morning Break)

CLARIFYING QUESTIONS FROM THE

COMMITTEE TO SPONSOR

DR. BURMAN: All right, why don't we get started? It's 10:10 a.m. For the next 20 minutes, until approximately 10:30 a.m., the Committee will have an opportunity to ask questions of the Sponsor and we thought the best way to do this is just open it up to the Committee at the moment and if you have a specific person on the Sponsor you want to answer that, please direct it, if not just direct it generally. Yes, Mike?

DR. PROSCHAN: This is for Dr. Daniels, who said that there is planned a clinical trial post marketing. I am wondering what will be the comparator in that trial?

DR. WOLF: The details of the design of that study are still under consideration, as Dr. Daniels described, the primary objective of that study is to demonstrate the clinical benefit of Saxagliptin going beyond simple glycemic control. So our intent is to work with the FDA and perhaps other health authorities to design that study.

DR. BURMAN: Thank you. Dr. Veltri?

DR. VELTRI: Yeah, this is for Bob Wolf. Bob, I was also intrigued as you mentioned about the hypothesis generating aspects of the data whether you looked at the various pooled analyses of primary MACE or custom MACE, it seems to be on a favorable side, obviously the hypothesis generating for which you are going to be testing in your upcoming outcome trial, and I wanted to just ask you, can you give us any information perhaps on any data you may have on proinflammatory markers that potentially could explain beyond just the hemoglobin A1c, potential benefits?

DR. WOLF: We have looked at proinflammatory markers in our program, we didn't see quantitative changes in those markers. I did want to mention though that, and this is very speculative of course, but some of the substrates of DPP-4 have been hypothesized to have cardioprotective effects and those substrates would include GLP-1, stromal cell derived factor-1 and perhaps even RANTES. I think that that's very speculative, the bottom line is to really properly assess as we intend to do a properly sized randomized control to really address the question directly.

DR. VELTRI: I guess the question I have, have you looked at for instance, HSCRP?

DR. WOLF: You know, we haven't seen a treatment affect an HSCRP.

DR. BURMAN: Thank you, Dr. Konstam?

DR. KONSTAM: Yeah, I have got a few questions. One is, I know this is principally about safety, but I sort of think about safety signals relative to the incremental clinical benefit that a drug might offer relative to other things in the market and I think the thing that one of the things you have stressed is the low potential for hypoglycemia, and I understand the concept of it very well. I just wondered if you can help me out

because I didn't really see evidence in the data set to support a claim I guess, that you have less propensity to hypoglycemia than other agents, in the signals that you presented, there was nothing worrisome about an excess amount of hypoglycemia, but nor was - did I see any support that you would be relatively less prone to hypoglycemia than other agents. Is that something you think you can defend based on the clinical data?

DR. WOLF: We agree with your assessment of the current data for Saxagliptin, it does not demonstrate any worrisome trends for hypoglycemia in primarily placebo-controlled trials. The proper way to assess that is do active control studies. We currently have an active control study ongoing, a head-to-head study against Sulfonylurea on top of Metformin and this study is long in duration and is ongoing at this time. So, one of the reasons that we are conducting the study is to address that very question.

DR. KONSTAM: All right. So at this point, it's really hard to make that statement definitively I guess.

DR. WOLF: It would be hard to make that statement relative to an active controlled trial. Our statements at the present time are based upon comparison to placebo primarily.

DR. KONSTAM: Okay. The second question I have is about your definition of primary MACE, and I just wonder if you could share with us how you came to it, I guess if I were thinking about it for the first time, I might think along - what I think was along the lines of thinking that the FDA followed that, let's start with SMQMI and go from there. You didn't do that and I just wonder if you could tell us how you got to that primary definition and is it really the first one you tried or, what can you tell us about that?

DR. WOLF: The way that we arrived at that definition is before we filed the NDA and before there was a lot of the discussion surrounding the people who are gamma agonists, we had to find an endpoint of acute CV events and that endpoint was defined by a list of preferred terms. When we began to engage with the FDA on focusing on MACE like events, what we did is we selected a subset of the preferred terms and defined acute CV events and these were preferred terms that focused on acute myocardial infarction, stroke, and cardiovascular causes of mortality. We did not do iterative definitions of events.

We selected that particular definition of MACE as our primary definition. The only other definition of MACE that we used was the definition that counted all deaths, not just cardiovascular deaths, and the reason for doing that is that we were concerned about any possible bias that might have been introduced by our assessment of cause of death. So when we included all deaths, not just CV related deaths, we essentially arrived at the same answer.

DR. KONSTAM: So the primary MACE definition is something you constructed and that was your first shot at it without any preconception about how the data was going to come out, is that what I hear?

DR. WOLF: That's right. Again, the method was based upon our original list of preferred terms that defined acute CV events, we subsetted those events to really focus on the events that were more consequential like MI and stroke.

DR. KONSTAM: All right. My last question relates to just making sure I understand the data and maybe the statistical folks in the room can help me with this because we are being asked to look at upper boundaries of confidence limits and I'm trying to reconcile, and I know we are going to have an FDA presentation, but I am trying

to reconcile the data that you presented with what's in the FDA documents and specifically looking at your, I guess it's slide 62, stratified analysis of FDA defined MACE, and looking specifically at the SMQ MACE, not the custom MACE. Then I go back - I go into the FDA document and what I am looking at is on page 37 of the FDA document table 16, I don't know if that's the best place to look or not, but, I am not - and maybe these are different analyses and they need to be clarified because your upper boundaries are lower than the FDA's upper boundaries and I don't know if somebody can help me reconcile, am I looking at the wrong things or?

DR. WOLF: I would ask the Agency to perhaps to comment on their methods. I believe that there were some differences in some of the methologic procedures. I know that in some cases the agency calculated odds ratios. Our analyses were primarily based upon risk ratios using the methods that we described.

DR. KONSTAM: I don't know if the Agency wants to comment?

DR. FLEGAL: Which estimates are you comparing from that table?

DR. KONSTAM: Well, I am just trying to figure out looking at the broad SMQ MACE definition and so I look at the ST plus LT number I get 1.42 for the upper boundary, for the odds ratio. So, are these just - and I don't know what they do.

DR. FLEGAL: Right. So that estimate would be most comparable to their bottom estimate, the incidence ratio which had an upper bound of 1.37 and but the exact method will generally give you a wider confidence interval, so that explains that difference of 0.05.

DR. KONSTAM: Okay.

DR. WOLF: If I could, we also use an exact method to calculate the risk ratio for the FDA defined endpoints. If I could please project slide 3-7, so in this slide, in

the middle of the description of each endpoint, there are two descriptions of the incidence rate ratio. The first one is based upon an exact method, for instance, rate ratio and the second for the Mantel-Haenszel. At least in our hands, these analyses give fairly comparable results for the upper bound the conference interval regardless of method.

DR. FLEGAL: Yeah, those are rate ratios.

DR. WOLF: Correct, yes.

DR. BURMAN: Thank you. Dr. Teerlink, did you have a question?

DR. TEERLINK: Yes, I actually have a - yes, I have a series of questions. So, it's a consistent theme in these diabetes presentations emphasizing how important the relationship is between diabetes and cardiovascular events and how this is really, really an important issue and we really need to know about this, and yet consistently, when you look at the enrollment criteria and event rates stay base, most of these trials are assiduous in excluding patients with cardiovascular disease and enrolling patients with extraordinarily low event rates. When I look at the inclusion ratios, there is - these exclusions of significant cardiovascular events within six months and heart failure and ejection fraction less than 40%.

So I assume since we have no experience in these patients that you are agreeing that Saxagliptin should be not given to any patient with a history of cardiovascular event within six months and not given to patients with heart failure either diastolic or systolic or any patient with an EF less than 40%, and since we have no experience in what happens to patients once they develop these things, that if a patient develops heart failure that they should be removed from Saxagliptin or if they have a cardiovascular event they should be removed from Saxagliptin for at least six months and then could be considered to be restarted on it. Do you have any - am I misinterpreting the

intent of your inclusion and exclusion criteria in the data set that we have before us, that's the first question.

DR. WOLF: I agree with you that we did exclude patients who had had a recent cardiovascular event from our clinical trial experience. We did look carefully at the incidents of cardiovascular events in subsets of patients who were at increased risk; even in those subsets of patients we did not see a signal for cardiovascular harm for Saxagliptin.

DR. TEERLINK: Based on 40 events?

DR. WOLF: Based on 40 events. As part of our plan going forward post approval we would - and we are planning a comprehensive set of studies including, pharmacoepidemiologic studies and additional randomized clinical trial studies as Dr. Daniels described in higher risk patients.

DR. TEERLINK: Okay, and related to that, what would be very useful is obviously one of the things that's in the recommendations from the diabetes guidelines is that it says specifically that program should include patients at high risk of cardiovascular events such as, patients with relatively advanced disease, elderly patients and patients with some lesser degree of - some degree of renal impairment, granted that it's for new clinical programs and so you don't technically fall under that requirement although, I guess that's part of what this committee meeting is about.

Nonetheless, it's still probably useful to see. I saw that you had only 15% of patients were above 65 years of age, and the majority of patients had duration of diabetes much less than five years. I would appreciate if you could preset more detail on the breakdown of the renal insufficiency experience where a breakdown of 80 millimeters per minute is not all that informative as well as a breakdown of the details that micro-

vascular complications that are present in this population. So if you could provide that data later that would be helpful. The final issue is – or if you have it now, I'm happy to say that now, I am sorry.

DR. WOLF: Are you asking for a description of the baseline characteristics of the population?

DR. TEERLINK: Yeah, breakdown of the renal - kind of breakdown better by more granularity in terms of the degree of renal failure and renal discomfort and renal insufficiency at baseline as well as a breakdown of the details of the micro-vascular complications at baseline.

DR. WOLF: So, approximately 15% to 16% of our population had mildly impaired renal function based on a Cockcroft Gault Equation?

DR. TEERLINK: Are you talking about, that's the 80 - less than 80 millimeters?

DR. WOLF: Yes.

DR. TEERLINK: Right, and what I am asking for is since that's extraordinarily mild, I don't think necessarily representative of the diabetes population as a whole that will eventually be treated. I'm asking for what experience do we have in patients who have, what's the breakdown of those patients who have a creatinine clearance less than 80 in little finer delineations?

DR. WOLF: So, most of those patients came into the range of a creatinine clearance between 50 to 80 and which would be in the mild range.

DR. TEERLINK: All right, if you could provide that data, that would be helpful. Finally, I am trying to figure out how - one of the major concerns of other agents you say that safety and tolerability of agents is a major concern and you mentioned that

that's largely due to cardiovascular issues, concerns about other agents along those lines, and I am confused then how if we are doing a post marketing study, the post marketing analysis compared to these other agents where one of the major concerns is cardiovascular events, how we are going to get any information on a post marketing study that's not randomized to comparing it to things where there is potential for cardiovascular concern, I don't know how I am going to be comforted by that?

DR. WOLF: We intend to do randomized clinical assessments of this issue.

DR. TEERLINK: Powered appropriately for cardiovascular endpoints?

DR. WOLF: Yes.

DR. TEERLINK: Thank you.

DR. BURMAN: Any questions?

(No response.)

I have some questions and I don't know who would be the best person. Some of them relate to physiology. The first question is a simple one, where does DPP-4 come from, which organ and related to that is, does it have any other actions and what happens in knockout mice where DPP-4 is knocked out?

DR. WOLF: I would like to ask Dr. Mark Curby to come to come to the podium please, or Dr. Garrell please. Thank you.

DR. GARRELL: So I am Mark Garrell from the University of Sydney. Could I get the questions repeated please, I think there was two or three.

DR. BURMAN: Of course. The first is what's the source of DPP-4 and the second is what other actions does it have and third is when you knockout mice for DPP-4 what other problems do they end up with?

DR. GARRELL: Okay. So the source of DPP-4 is it's a ubiquitous enzyme. It's made by lymphocytes, endothelial cells, epithelial cells. So it's throughout the body. It's on the surface of cells. It's released into the serum and extracellular, it's actual function has never been entirely clear. It appears to have a widespread function in inactivating small peptides by cleaving a small bit of the N-terminus, and the number of peptides is about two dozen that's has been identified as being targets of this enzyme.

What happens in vivo is that namely four peptides have been found to be physiological substrates, that is they are inactivated in vivo. The other issue about targets in vivo is that there are other enzymes present that inactivate those particular targets. So, the reason I guess what you are getting at is the reason why GLP-1 or GIP are the most important targets and therefore have the inhibiting DPP-4 has efficacy for type 2 diabetes, and it appears to be because as was mentioned at the start that GLP-1 is inactivated very rapidly by DPP-4, that's two to four minutes. So when you inactivate it, the next enzyme that comes along which is an endopeptidase which when activated, takes a whole lot longer, it takes 10 hours. So, that's apparently where the efficacy comes in. Now the other question about knockout mice, I have been breeding the knockout mice for more than 10 years without seeing any detrimental effects in them.

DR. BURMAN: One other quick question, I know the committee has one as well, and that relates to are there any other adverse pathophysiologic effects in animals or humans of elevating GLP-1 other than the ones you are talking about related to diabetes?

DR. WOLF: We are not aware of any.

DR. BURMAN: Thank you. Dr. Wyne, did you have a question?

DR. WYNE: Yes. I had two questions related to Dr. Teerlink's questions and one was just a follow on related to the event driven trial that you have mentioned, and my question was are the events driving this, are they going to be macro-vascular events; micro-vascular events or both? The reason I am asking is obviously we are all interested in a CV outcomes trial. Glucose control hasn't been shown to decrease macro-vascular events. It has been shown to decrease micro-vascular events and we are assuming that that is the same for this class of agents, which have not yet been shown to decrease micro-vascular events. So I am just curious what these events actually are going to be.

DR. WOLF: Again, the design of that study is still under discussion. We think that studying macro-vascular events will make an important contribution in the area of type 2 diabetes. So we are at this time focused on making certain studies properly sized and designed to address that issue because that would make the most important contribution to the field.

DR. WYNE: Thank you, and my other question is just trying as he was to understand a little bit better the cardiovascular risk level of these patients, and I just had a couple of specific questions. When you reported the percent that had hypercholesterolemia, was that based on their reported past medical history or their baseline lipid profile at entry?

DR. WOLF: That was based upon the reported past medical history by the patient.

DR. WYNE: Okay. Do you know what percent were on Statins and whether or not there was any specific Statin used at a high level in either of the specific studies or the global population?

DR. WOLF: We will get the data for you on the percent use of Statin and the second question?

DR. WYNE: Just if there was any specific Statins, I guess to go with it is actually the Statin-fibrate combination also.

DR. WOLF: We will have to look at that during the break.

DR. WYNE: Okay, thank you.

DR. BURMAN: Thank you. One more question Mike.

DR. PROSCHAN: With respect to all those different cardiovascular outcomes you have had, were any of the tests for heterogeneity of the risk ratios, did any of those come out significant? I think I know the answer to this.

DR. WOLF: I think I will ask Dr. Dave Henry to come to the podium to address that question.

DR. HENRY: David Henry, Biostatistics, Bristol-Myers Squibb. This is with regards to the sub-groups. Due to the small number of events within the sub-groups, one would not expect, there to be power to observe interactions that might be clinically relevant and we did not see any.

DR. BURMAN: Thank you very much.

DR. WOLF: If I could, I just wanted to finish a response to one of the questions that we had earlier, I wanted the committee to be aware that the Sponsors are currently conducting a randomized clinical trial in patients with moderate and severe renal sufficiency. Those data, I mean that study is still ongoing at this time.

DR. BURMAN: Thank you. We will now proceed with our presentation from the FDA. I would like to remind public observers at this meeting that while this

meeting is open for public observation, public attendees may not participate except with the specific request of the panel. Dr. Lowy is presenting.

FDA PRESENTATIONS

NAOMI LOWY, M.D.

Good morning, Mr. Chairman, members of the Committee, Ladies and gentlemen. This morning I along with the FDA statistician will be presenting the results of the MACE analyses performed. To give you an overview of what I will be discussing, I will briefly introduce Saxagliptin outlined as clinical development program and detail the common phase 2I study design. I will then go into subject demographics and disposition and subject exposure. I will then present the core of this talk the MACE analysis, which will include a presentation by the FDA statistician and a brief summary will conclude the presentation. As much of this information in the next few slides is already been presented this morning, I will be brief.

Saxagliptin is an oral Dipeptidyl peptidase-4 inhibitor and Bristol-Myers Squibb is seeking an indication for Saxagliptin as an adjunct to diet and exercise to improve glycemic control in patients with type 2 Diabetes Mellitus. DPP-4 is the enzyme responsible for inactivation of GLP-1 and GIP, the incretin hormones, and in response to an enteral glucose challenge, the ingredients are gut hormones that regulate postprandial glucose excursion in a glucose dependent manner. Incretins regulate postprandial glucose excursion both by increasing Insulin secretion and decreasing glucagon release. This effect is glucose dependent, hypoglycemia is minimized. Januvia is currently the only FDA approved DPP-4 inhibitor.

The phase 2b3 program included in the NDA is comprised of eight studies. Six are phase 2I studies in which the main study period was 24 weeks, a phase-

2b dose finding study and a phase 2I mechanism of action study. While the bulk of data arises from the core phase 2I studies, the safety data that will be presented includes all eight studies. These two studies were of shorter duration and enrolled smaller numbers of subjects and therefore contribute less.

Now specifically focusing on the core phase 2I studies, all six were comprised of what the Sponsor termed short-term and long-term periods; the long-term period essentially being an extension phase. At the time of the NDA submission, the long-term periods were still ongoing. Still data from the long-term periods were included in the NDA and the 120-day safety update. All six-core phase 2I studies shared a common study design. A screening period followed by a placebo lead-in period and then a 24-week so called short-term period. The FDA draft guidance on diabetes from February 2008 refers to the six-month placebo controlled phase as well as an extension phase of six to twelve months, which the Sponsor has termed the long-term period.

In this clinical development program, the extension or long-term phase was notable and the double blind treatment was continued along with open label rescue medication that I will detail in upcoming slides. The Sponsor incorporated a rescue scheme in the short-term and long-term periods for subjects with inadequate glycemic control on their randomized treatment. Therefore subjects could enter the long-term period in one of two ways, by either completing the 24 week short-term period without requiring rescue, or secondly requiring rescue during the 24 week short-term period and then entering the long-term period.

For rescued subjects, treatment in the long-term period remained double-blind in addition to open label rescue. The long-term period was not voluntary and the subjects were not asked at the end of the short-term period whether they wanted to

continue. The Sponsor chose three doses of Saxagliptin to be used in the phase 2I program, 2.5 milligrams, 5 milligrams, which is the proposed marketing dose and 10 milligrams. These are the actual core phase 2I studies.

There were two monotherapy studies, three add-on combination studies, one add-on to Metformin, one add-on to sulphonylurea and one add-on to thiazolidinedione, and finally one initial combination with Metformin study. Both the monotherapy studies and the initial combination with Metformin studies enrolled treatment naive type 2 diabetics. These phase 2I studies also had a common primary efficacy endpoint, which was the change in hemoglobin A1c from baseline to week 24.

I mentioned earlier that rescue criteria for uncontrolled hyperglycemia were incorporated both in the short-term and long-term periods. Therefore subjects could be rescued at any point. Here I show that the rescue criteria differed between these two periods. Rescue in the short-term period was based on fasting plasma glucose ranging from 200 to 240, while rescue in the long-term was based on hemoglobin A1c ranging from 7% to 8%. The details of the rescue criteria are contained in your briefing document, but I will point out that the cut off values dependent on the study week becoming more stringent as the study progressed.

I have listed here the specific rescue medications used, which were the same in the short-term and long-term periods. These included Metformin and thioglitazone, both of which were titratable. Now I will present the baseline demographic data for subjects in the phase 2b3 program. While your briefing document contains a more comprehensive list, here I will summarize age, duration of diabetes, history of coronary artery disease and previous diabetes treatment. My intention in presenting these is for you to understand the cardiovascular risk of the population studied. This risk is

important when interpreting the Forest plots that will be shown in the statistical presentation. Because these are the major contributor to the Forest plots, I will be presenting the study separately as un-pool data. Within each study however, the treatment groups are pooled since they were well balanced.

Here is the demographic data for the two monotherapy studies. The mean age was low to mid 50s, subjects had diabetes for a mean of two to three years and in study 11, 2.5% of subjects had prior diabetes treatment while 5% of subjects in study 38 had prior treatment. The history of coronary artery disease reported was approximately 5% in study 11 and was higher at 13% in study 38. This is the demographic data for subjects in the initial combination with Metformin study with data fairly consistent with those seen in the monotherapy studies. Again, the mean age was 52 years, subjects had duration of diabetes of 1.7 years, 8% of subjects had a history of coronary artery disease and 2% reported previous diabetes treatment.

Finally, the demographic data for the three add-on combination studies. The main differences from previous slides are the duration of diabetes and previous diabetes treatment. The duration of diabetes-ranged from five to 6.9 years which we would expect as these subjects entered the study already on medical therapy. Therefore 100% of these subjects had previous diabetes treatment.

I will next present disposition data emphasizing the short-term period here since the MACE analysis will rely heavily on the short-term periods as well as the short-term plus long-term periods. It is important to remember that the short-term safety data includes subjects who have not been rescued. Across all the core phase 2I studies, 74% of subjects completed the short-term period. The majority of dropouts were due to rescue. I would reiterate that these were not typical dropouts since they continued on

randomized treatment with open label rescue, and this clearly has important implications versus an overt open label extension. As representatives for the core phase 2I studies, I will show the disposition data for one monotherapy study as well as the add-on combination studies.

Here is a graphical representation of the short-term disposition data for monotherapy study 11. At week 24, approximately 70% of subjects in the Saxagliptin treatment groups remained while this was approximately 58% for placebo subjects. Within the Saxagliptin groups, no dose response was seen. These are graphs for the three add-on combination studies. In the add-on to Metformin study, approximately 75% of subjects were retained in the short-term period by week 24 while only 63% of placebo subjects remained. In the add-on to Glyburide study, 77% of the Saxagliptin treated subjects remained at the end of the short-term period, while this was 66% for placebo. Interestingly, for the add-on to TCD studies the numbers were similar for Saxagliptin treated and placebo subjects, both around 80%.

The proportion of randomized subjects who entered the long-term period ranged from 78 to 90%. While I will not go into detail about disposition into the long-term periods since they are still ongoing, I will mention that as of the 120-day safety update, 50 to 58% of subjects in the monotherapy studies remained in the long-term period, 29 to 77% remained in the add-on combination studies and 66 to 77% of subjects remained in the long-term period of the initial combination with Metformin study.

Next I will present exposure data for subjects who were treated with Saxagliptin. As was with the demographic data, the exposure data is of particular relevance when interpreting Forest plots to be shown later in the statistical presentation. The analyses performed by FDA in the applicant were based on exposures from the short-

term and long-term periods. Therefore this includes rescued subjects and data from the 120-day safety update. This slide summarizes the exposure in Saxagliptin treated subjects.

To put this into context for you, the FDA Draft Guidance for diabetes published in February of 2008 recommends that phase 2I trial data for drugs developed for type 2 two diabetes be available for at least 2500 subjects exposed to the investigational product with at least 1300 to 1500 of these subjects exposed for one year or more and at least 300 to 500 exposed to the product for 18 months or more. I show you this slide to confirm that the Sponsor met these recommendations.

These are box plots that show exposure for each of the studies used in the MACE analysis. These lines represent the median exposure and these represent the full range of exposure. We can see that monotherapy study 11 and that the add-on to Metformin study 14 have the greatest exposures, both around 90 and 100 weeks. While studies eight and 41, the phase 2b and the phase 3 mechanism of action studies have the lowest exposures. The remaining studies had fairly consistent exposures.

I will now delve into the core of the presentation of the MACE analyses. The database for the requested MACE analyses consists of the eight phase 2b3 studies already mentioned. Seven of the eight are placebo controlled. The initial combination with Metformin study contained active and placebo comparisons. The analyses requested by FDA were performed on the following. The short-term 24-week period alone which excludes data collected after glycemic rescue, and then the short-term plus long-term data, which does include data following the initiation of rescue therapy. Again subjects who continued into the long-term period remained on double-blind randomized treatment.

FDA requested two separate endpoints be analyzed for these populations and the intent of choosing these endpoints was twofold. First, to broadly capture all possible strokes and myocardial infarctions and secondly to more specifically include terms which when chosen by the investigator were likely to represent true myocardial infarction or stroke. It is with this intent that the agency termed these endpoints, broad SMQ MACE and custom. These endpoints separately with the addition of cardiovascular deaths were thus chosen as the MACE endpoints of interest.

I will now more specifically define each of these endpoints. The so called broad SMQ MACE endpoint is a composite endpoint that included all cardiovascular deaths and all preferred terms in the SMQ for myocardial infarction and central nervous system hemorrhages and cerebrovascular accidents. On the other hand, the so-called custom MACE is essentially a subset of the broad SMQ MACE. It was developed by collaboration and consensus of three FDA reviewers.

In defining these endpoints, we selected terms, which seemed highly likely to represent events that would truly be an MI or stroke and that represented events, which were acute and atherosclerotic in mechanism. The complete list of all terms used on both endpoints is included in your briefing document. Here, I provide examples of which terms were chosen for these two endpoints. Under myocardial infarction terms, acute MI was chosen for both the broad and custom endpoints while blood CPK increased was listed only under broad. Under stroke terms, CVA was listed under both endpoints, while paralysis was chosen for broad only.

I will now start presenting results of the analyses. In this slide, I present the incidence of custom MACE data for all treatment groups, for both the short-term and short-term plus long-term periods. These numbers represent the first event for a subject.

Overall, there were a few events noticed, one event here, one event here, two events here. In the short-term period, only the Saxagliptin treatment groups had incidences of less than 0.1% to 0.2% versus 0.6% in the comparator. In the short-term plus long-term periods, overall events remained low with incidences of 0.5% to 1.1% in the Saxagliptin groups versus 1.4% in the comparator group.

This is the same data I have just shown. However, all of the Saxagliptin groups are pooled. Therefore the incidence of "Custom MACE" events in the all Saxagliptin group for the short-term period is 0.1% versus 0.6% in the comparator, and 0.7% in all Saxagliptin groups versus 1.4% in the comparator for the short-term plus long-term period. Note that there are twice as many subjects in the Saxagliptin groups versus placebo, even when patient years were taken into account, the results were consistent.

Again this is the same data I have been showing you but now broken down by System Organ Class or SOC for the short-term period. The majority of "Custom MACE" events in the short-term period fell into the cardiac disorders SOC, with 0.1% of subjects in the 10 milligram group versus 0.4% in the comparator group. Under nervous system disorders, events were balanced across all groups with an incidence of less than 0.1% or 0.1% throughout.

Again, the same data but now I zoom in on the cardiac disorders SOC have listed all the preferred terms that occurred under that SOC which were four. Only one myocardial infarction occurred in a Saxagliptin treated subject, while each of these events occurred at least once in the comparator group. Here is the breakdown of preferred terms under the nervous system disorders SOC for the short-term period. CVA

was observed only once in the 2.5 milligram, 5 milligram and comparator groups, while hemorrhagic stroke was seen once in the 10-milligram group.

So far, I have discussed the incidences of events under the "Custom MACE" endpoint. I will now present the incidents of "MACE" events using the broad SMQ endpoint. Again, overall event rates were relatively low. In the short-term period, 1.4 to 1.9% in the Saxagliptin groups versus 2% in the comparator. In the short-term plus long-term period, rates were similar across all groups, all around 3%. Again the same data with the Saxagliptin groups pooled showing you an incidence rate of 1.7% versus 2% in the short-term period and similar rates of 3 and 3.2% in the combined short-term plus long-term periods. When these events are then broken down by SOC for the short-term period; it is clear that one SOC investigations which I have highlighted, contains most of the events with incidence rates of 1.1 to 1.6%.

To illustrate the point that the SOC investigations, comprises the majority of events in the broad SMQ analysis, I am now showing the preferred terms under the SOC of investigations. It is the term blood CPK increased that clearly drives the number of events seen on the broad SMQ analysis with the rates ranging from 1.5% in the comparator group to 2.2% in the 5-milligram group. Just as a reminder, increased CPK was not included in the "Custom MACE" endpoint. The FDA statistician, Ms. Mele, will now present the statistical analyses of these MACE events.

FDA PRESENTATIONS

JOY MELE, M.S.

Thank you. Thank you, Dr. Lowy. Now you have seen the MACE results from the company and our results do not differ from those results in any notable way. So in addition to showing you these results again with some other details, I will describe to

you some of the issues we considered when planning the MACE analyses, including the choice of statistical methods. Then I will present the results starting with an overview followed by some specifics about the SMQ in "Custom MACE" results. At the end of my talk I will show some sub group results.

When planning the MACE analyses, there were three issues we considered: the endpoints, the treatment periods, and the methods. You have already heard a lot of information about these issues. I am going to mention a few statistical aspects. You have heard from several speakers detailing about the two endpoints defined by FDA. Because these endpoints were not adjudicated, and were defined post talk, there was an effort to capture any cardiovascular signal by including a broad endpoint. With the SMQ endpoint, we are aiming to show consistency of a fact with the custom endpoint. Adjusting from multiple endpoints though is not an issue because it is the "Custom MACE" endpoint, which is of primary concern.

With regard to the time period to use in our analyses, we considered the impact of the use of open label rescue medication. About one-third of the patients in these trials entered the long-term period on rescue medication and rescue was generally higher in the placebo groups. So, we wondered about the influence of rescue on followup. The addition of low dose rescue medication in the long-term period may or may not bias towards the alternative hypothesis that of showing non inferiority when looking at these cardiovascular endpoints. So, we decided we should look at both the short-term period where no events on rescue medication are captured and also look at the short-term plus long-term period.

About 85% of the patients continue to be followed on double-blind treatment into the long-term period and so the randomized groups were largely preserved.

Lastly, we thought it was important to analyze the results with more than one statistical method. From our experience with Avandia and other drugs, we knew that the method used could impact the results particularly with rare events and with multiple studies with no events.

Now here are the estimates we considered. All these estimates are computed stratifying on study. I will explain what each of these offers to the interpretation of the CV results. For the risk difference, studies with no events are included in the analysis. This contrasts with methods for computing odds ratios where studies with no events are only included if a continuity correction is used. With the risk difference, we are able to assess the influence of the no event trials on the interpretation of risk when we look at this estimate against an odds ratio.

The incidence rate ratio, that is the second one listed here, is computed based on person years of exposure. So if there is differential exposure between treatment groups, the computation of this estimate adjusts for that difference. With low event rates and small differences in exposure, this estimate will not differ from a risk ratio computed as the ratio of incidences. For Saxagliptin, we thought this estimate was important for the short-term data where dropouts were generally significantly greater in the placebo group than the Saxagliptin group, and not as important for the short-term plus long-term period, although we will show estimates from both of the time periods.

Now the estimate we use for assessing risk in the context of the boundary set by the guidance was the odds ratio based on an exact test. Our summaries all contain these estimates. The confidence interval for this estimate tends to be conservative compared to intervals computed by other methods and therefore I think an attractive approach for assessing CV risk.

So here are the stratified common odds ratios and 95% confidence intervals for the overall MACE results. Now I have drawn three lines on the graph, one at 1 and then one at 1.3 and 1.8. You can see we have the two estimates depicted on this graph. All the plots of the odds ratio that I will show contain a line at one and so estimates to the left of the line indicate results favorable to Saxagliptin, and estimates to the right are unfavorable. Now in addition to the short-term plus long-term results that you saw in the companies presentation, that is noted here as ST plus LT, we are depicting here the results from the 24 week short-term period. That is ST. The message though is the same regardless of which time period you use. The "Custom MACE" upper limit is well under 1.8 and close to one. The upper limit of the broader endpoint is also less than 1.8 and a little above 1.3.

Now we would like to show you some specifics about these results. I will first cover the SMQ results, and then the "Custom MACE" results. Now here I am showing you the results for SMQ using the three estimates I mentioned earlier. At the top is the risk difference, and here is the scale for the risk difference that goes from –1% to 1%. The scale for the ratios is a log scale and it goes from 0.02 to 5. Now it's very clear that there is no difference between the rate ratio and the odds ratio results, that's with these estimates, and that all the results present produce estimates that are close to this no difference line.

Now here is the Forest plot of the SMQ results using the full exposure. I have listed the studies in numerical order with the incidences to note here and then the odds ratios. I want to point out that there are no trials without events. The bulk of the events come from the course studies, so are these trials with the 12-week studies depicted at each end of the graph. Dr. Lowy described some of the events that were observed for

the SMQ endpoint. She mentioned how the majority of the events were recorded as increased CPK; 50 of the 58 SMQ events for Saxagliptin and 14 of the 25 for placebo. We thought it was important to do an analysis without these events.

So using the raw adverse event data, I looked to see if patients with the CPK increases had a subsequent SMQ event and found only one placebo patient with such an event. The reanalysis of SMQ without these events results in an odds ratio much closer to the one observed for "custom MACE" and for the company's Primary MACE endpoint and that's this estimate depicted here. So the estimate is about 0.5 with an upper bound of about one, and you can see the difference between when you include the CPK increases.

So now let's look more closely at the custom MACE results. Here are the three different estimates of risk for custom MACE. The message is quite clear that there is no evidence of increased risk based on these estimates. The only difference we see is that the ratio results are borderline significant, that's these results, while the risk difference results are not. They are not statistically significant. This difference may be due to the fact that the three trials had no custom MACE events.

So we will look next to the Forest plot. I am showing you first a Forest plot of the custom MACE results using the short-term data. I wanted to show you this because we initially thought that our focus would be primarily on the short-term data and not the short-term plus long-term data. For this plot, a half is added to each cell of the corresponding two by two table of studies with no events in at least one arm. This addition called a continuity correction enables one to compute an odds ratio for these studies and also allows one to compute an overall estimate including all eight studies. For seven of the eight studies, three of which had no events, a continuity correction is

used. There is only one study with events in both treatment arms, and that study is 39, it has the largest symbol here, which is the study of initial combination of Saxagliptin with Metformin. There are five events in this one study, and there are only a total of 11 events in all eight studies.

Now the estimate using the continuity correction is 0.3 which differs from the one we get when we do an exact test which is 0.2 and this is not surprising, because when you use a continuity correction the estimates tends to shift towards the not. Notice there is only one study that produces an estimate greater than one. That's study 13. Study 13 is the study where patients treated at time of enrolment with TZD, either Pioglitazone or Rosiglitazone, are randomized to add-on therapy of Saxagliptin or placebo. So overall we see the plot suggests no significant heterogeneity across the trails and test for heterogeneity support that.

Now let's look at the short-term plus long-term data for the custom MACE endpoint. The only difference here is that there are more events. Instead of a total of 11 events, there are now 40 events. So generally the confidence limits are tighter for the individual study odds ratios and the overall odds ratio. Again we see that study 13 produces an estimate greater than one. Now because of all the discussion around the TZDs and CV events, we thought we should look at those events by background TZD. This table shows you the custom events by treatment group for both doses studied and by background TZD and you can see there is nothing here that differentiates the TZDs for these few events.

Lastly, I would like to show you some subgroup results using the custom MACE endpoint for the short-term plus long-term data. We did these analyses because we wanted some reassurance that the results seeing in an overall population of rather low

risk would also be seen in a higher risk subgroup. I am showing here the results by type of study, here at the top by gender and by age. As Dr. Lowy showed earlier, the add-on studies were comprised of patients who had a longer history of diabetes than the patients in the monotherapy trials and all had been previously treated with anti diabetic drugs. So the control event rate of one is much higher for those studies in monotherapy. The control event rate is 1.8% for the add-on trials compared to six times - which is about six times the rate seen for the monotherapy trials, but what we see is that the odds ratios are essentially the same.

For gender and age test for inner actions yielded P values under 0.2 suggesting some treatment effect differences between males and females, and younger and older. Actually the estimate for males and females was about 0.11 and 0.17 for this comparison. I want to point out that none of these estimates provide evidence of significant increased risk. I also would like to add at the end here that the analyses by FDA pharmacologists' suggested higher exposure based on AUC for elderly patients than younger patients. Thank you for your attention and now Dr. Lowy will return to summarize.

DR. LOWY: The Sponsors own initial MACE analysis has already been mentioned. I summarize with this slide to place the FDA requested analyses in the context of the Sponsors analysis, particularly when comparing the point estimate of 0.5, an upper limit of 1.2 in the Sponsors analysis, to the custom MACE numbers already presented. A consistency of results is seen. Therefore, in summary, we have shown you that patient populations were comparable across the studies used in the MACE analysis. With this, low event rates were seen in all studies. Consistent results for Custom MACE and SMQ broad MACE were seen particularly when excluding the preferred term of

increased CPK. Short-term and long-term results including the followup of rescued subjects were consistent with the short-term results.

The MACE results were not dependent on the statistical method used. Finally, analyses of all endpoints yielded estimates of common odds ratio less than one, and upper bounds for the 95% confidence interval of less than 1.8. Thank you.

CLARIFYING QUESTIONS FROM THE COMMITTEE TO FDA

DR. BURMAN: Thank you both very much. We would like to open the floor up now for discussion by the committee and specifically questions to any of the members of the FDA who presented this morning, including Dr. Joffe.

DR. FLEGAL: I would like to understand a little better what the reason was for developing the custom MACE. It wasn't clear to me whether this was done before looking at the data or whether there was some feature of the data that led to the development of the custom MACE, and a sort of related question maybe, is this idea of a reassuring point estimate, I wasn't sure what was actually meant by that?

DR. JOFFE: Let me speak first to those custom MACE endpoint. The custom MACE endpoint and the broad SMQ MACE endpoint were both defined before looking at any of the data. The broad SMQ endpoint used standard SMQs for myocardial infarction, the central nervous system hemorrhages and infarctions and cardiovascular death, but there was concern when looking just at the broad SMQ MACE that some of the events that are included in that standard endpoint, although they could be consistent with an acute important cardiovascular event, they may not necessarily represent such an event in some patients. So to try and pair that down, three clinical reviewers came up with, they looked through all those preferred terms and picked out the ones that they

thought would most likely represent an acute important cardiovascular event as reported by the investigator.

Now that was done just looking at preferred terms without knowing what events occurred in the clinical programs and those were the analyses that FDA requested of the company. For this reassuring point estimate to prevent myself from getting into trouble with the statisticians, I'll ask them perhaps to - if they have a comment on that.

DR. MELE: I'm not quite sure at what point in time we said reassuring the point estimate. Was it in Hilton's presentation?

DR. FLEGAL: Yes, the guidance uses the term reassuring point estimate.

DR. JOFFE: Maybe I will start speaking about that. The point with the guidance although I know there has been some statistical discussions about this, is that if you just focus on the upper bound of the 95% confidence interval and you don't take into account the rest of the confidence interval and where the point estimate falls, which is our best guess of what the treatment is effected based on that sample data that you may be missing something and so, for example the guidance says an example that if a point estimate was 1.5, even if your upper bound was 1.8 and your lower bound was above 1, that wouldn't be as reassuring as if your point estimate fell around unity with the upper bound of 1.8.

DR. FLEGAL: Can I follow up on that because the slide says that if you have upper bound of 1.3 with a reassuring point estimate, then a post marketing trial would generally not be necessary. So in that context, the reassuring point estimate would be something below one I suppose would be reassuring, about...

DR. JOFFE: Close to one.

DR. FLEGAL: Close to one, but no specific definition?

DR. JOFFE: Right.

DR. FLEGAL: Thanks.

DR. PROSCHAN: Yeah, I think this is sort of like trying to define what's beyond a reasonable doubt and the judge always says, well it's, if you don't have a reasonable doubt or something, it's hard to pin it down, and I think the guidelines, the 1.8, my recollection of that advisory committee meeting was that the statisticians, myself and Tom Fleming were trying to get it more instead of saying, ruling out 1.8 which isn't ruling out much. I mean that's, ruling out something as harmful as 1.8 is not saying a whole lot.

That still allows something that's very harmful to get in. So I think what we were trying to do was make a statement where we lowered the confidence level, instead of being 95% confident maybe 80% and then translating that into, so we have to be 80% confident, but now we are ruling out 1.4, something like that. So I think this idea of ruling out a 1.8 and feeling somehow confident about that is really not saying a whole lot. On the other hand, I don't know, whether I, this is not really a question. So maybe I should shut up now.

DR. BURMAN: We will have much more time in the afternoon for discussion. Anything you like to say of course. Dr. Teerlink, you had a question and then we will go to Dr. Veltri.

DR. TEERLINK: Yes, the question was in regards to, it's interesting to see in the custom MACE and, I am interested because you always yell about how you can never do subgroup analyses on small numbers and here we are doing multiple subgroup analysis on 40 events at an event rate that's barely 1%, but that being said, the one analysis where you finally get to what is potentially a high-risk group, which is the

patients who are above 65, that's where it starts to shift over to the other direction. Is there anything that we have and to - and granted with huge confidence intervals, but that's just because we have no events.

Do we have anything in terms of previous duration of diabetes? Given that most of these cardiovascular events, the increased risk of cardiovascular events doesn't really start occurring in patients with diabetes until they have had diabetes for ten years. Do we have in the group who had diabetes for ten years or more any evidence of what happens with those patients?

DR. MELE: We didn't specifically look at duration, but we just broke it down by the two types of studies which does sort of get you there, but doesn't look at the upper end.

DR. TEERLINK: I mean differences like from two years to five years, right?

DR. MELE: Right, we couldn't keep going breaking it down because of the fact that you do have so few events. I mean, once you got to over ten, you are going to have, I don't know what the number is, but it is going to be so few events, it is not going to be worth analyzing.

DR. TEERLINK: The point being there are almost no patients in this trial who have had diabetes for more than ten years in the entire development program.

DR. MELE: Exactly, right.

DR. BURMAN: Thank you. Dr. Veltri.

DR. VELTRI: Yeah a comment and a question. I gather we find ourselves here because obviously there wasn't any prospect of adjudication of events and really what we are trying to do here is to get a better sense of the reality I guess of what

those events were albeit there weren't as many as for whatever reason, population, length of duration of followup etcetera.

So, a custom MACE algorithm was developed and my question is since there are large databases of clinical outcome trials I am sure the FDA has, where there has been CEC adjudicated not simply investigated reported events, has there been any look at how predictive, what's the sensitivity and specificity of this custom MACE definition in those types of databases to kind of get some comfort as to how reliable, because it seems as though the primary MACE is done by the Sponsor and the custom MACE is done by the FDA, are very similar, basically point estimate and upward bounds?

DR. PARKS: To answer your specific question, no, the custom MACE has not been a value in the context of other large cardiovascular outcomes trials where they have been prospectively evaluated for cardiovascular endpoints. If I can take a moment to just clarify and answer to Dr. Flegal earlier, as to how the agency came up with custom MACE and the broad SMQ MACE, part of it was as the applicant had presented that when they, I believe it was in December, you provided to us your MACE analysis, and the agency did ask both applicants to provide their MACE analysis and was a recognition that these two applications had very different approaches to providing a MACE analysis to us. Recognizing that if we are now holding this guidance, let's call them the guideposts for ruling out a cardiovascular risk, it was important that we apply some sort of uniform approach. That is why the custom MACE analysis the definition was established and applied equally to both companies.

DR. BURMAN: Thank you for the explanation. Any other questions from the Committee?

(No response.)

I have one question for the FDA, which is a general one. I am not sure I understand exactly. I would like a little more discussion of the elevated CPK, because although other things certainly can elevate, other conditions can elevate CPK, in this circumstance, usually it's going to be a myocardial infarction or at least some sort of cardiac damage, so much of the difference between the broad SMQ and a custom MACE related to people with elevated CPKs.

I believe it was Dr. Mele who presented data that said, if someone had an elevated - when they analyze people with elevated CPKs, most of them did not have another event, if I understood that correctly, which isn't really directly answering the question that they have an event when we are analyzing them. It makes a big difference in the analysis whether you focus on the custom MACE or the broad MACE, or the broad SMQ. So could you speak a little more about the CPKs and were there any other evidence that these people actually had heart disease at the time?

DR. MELE: I just want to clarify about that analysis. Dr. Lowy will answer your question that it didn't have to just be a subsequent event. It's just did they have an event that was other than just a CPK, but these are first events. So the CPK would be the first event that was observed and then you would have to look for subsequent events.

DR. BURMAN: This was an elevated CPK when people just were analyzed or they came in the hospital for chest pain, or how - what were the clinical circumstances of an elevated CPK?

DR. LOWY: So, just to reiterate, these trials were not prospectively designed to pick up these events. So a lot of the information that we had regarding these

events of increased CPK, the information was fairly limited. Another thing to point out was these CPK elevations in general were not serious adverse events; again, giving us limited information. In general, these were elevated CPKs found on study visits in which blood was drawn and the increased CPKs were found and reported to be an adverse event by these individual investigators.

Given all those constraints, we did recently take a look at whatever information we had regarding the increased CPKs and the most information we could find in connection was those subjects who were discontinued because of increased CPKs. Those were subjects that had narratives. From those narratives that we reviewed, these did not appear to be cardiac events. I don't have a full listing of them, but in general, again they were random CPK elevations associated with exercise, associated with possible Statin use, but again, there was no suggestion that these were cardiac events.

DR. BURMAN: One more question on that if I might, do you have any idea what percentage of these people who had elevated CPKs were on Statins?

DR. LOWRY: I don't have the exact information. In regards to the question that was asked before regarding how many of the subjects in general in this development program were on Statins, I'm not sure if the Sponsor yet has that information, but for instance, in the monotherapy studies, I can say at least study 11, I believe about a third of patients were on cholesterol medications with the use of Statins was about 8%, anywhere from 7% to 10%. So again overall, fairly low, but I don't have that exact information about how many of those increased CPKs were associated with Statin use. They were certainly not all of them.

DR. BURMAN: Thank you. The Sponsor had a comment?

DR. WOLF: Since the Sponsor sent the SMQ MACE events, the primary MACE events in all depths for external review, I think it might be useful to have Dr. John Alexander define some perspective on the SMQ MACE and the CK increases.

DR. ALEXANDER: Thank you. So I'm John Alexander. I'm a cardiologist from Duke and approximately four weeks ago, BMS approached me and my colleague, Ken Mahaffy, to review the data that was available on all of these SMQ MACE events, and I reviewed half of them and Ken Mahaffy reviewed the other half. We used our standard clinical event committee processes using pretty standard cardiovascular trial definitions for stroke, myocardial infarction and cardiovascular death. I think there has been a good discussion about these elevated CK levels.

My understanding is that there were, protocol mandated blood draws at routine study visits that were sent to a core lab and had elevated CKs and were sent back to the investigators asking about whether there were adverse events. In the vast majority of these, first of all the documentation was limited mostly because the patients were asymptomatic. A handful of them had some report of some trauma or vigorous exercise or something, and the majority of them had - the actual electrocardiograms weren't available, but reportedly had normal electrocardiograms on multiple occasions after these events. So that's the elevated CK samples.

The cardiovascular events, the things that went into primary and custom MACE actually had pretty good documentation in that they were real cardiovascular events. If we had been doing prospective clinical event adjudication of those events, virtually all of them, we would have called real clinical events, but the isolated elevated CK values which again typically actually occurred on multiple occasions in these

patients, on multiple separate blood draws, are in my judgment hard to conclude or hard cardiovascular events. Thank you.

DR. BURMAN: Thank you. I would like to point out for the record that the FDA in my understanding has not had a chance to review the Duke evaluation, but has reviewed the previous information. Is that correct?

DR. TRAN: Yes.

DR. BURMAN: Thank you. Any other comments on that? Okay, thank you. Then Dr. Wyne I think is next. Did you have a question?

DR. WYNE: No.

DR. BURMAN: No. Okay. Then Dr. Konstam.

DR. KONSTAM: Well I just wanted to comment on this discussion because I guess you can't have your cake and eat it too here. I think the FDA did a really terrific job of explaining how they got there with regard to these different endpoint definitions and did it without any bias based on what actually the data showed. I think they did a very nice job of showing, of describing the pros and cons of the SMQ MACE versus the custom MACE.

The custom MACE is more specific and if we had I guess enough events to be really comfortable with that, we could have stopped there, but for my money, the broader term has the value that it has more events in it. So when we get to the point of really trying to dissect what the actual real upper boundary is here, you know, I guess you wind up using the broader term with all it's vagaries and all it's problems and all the non specificity to develop some reassurance about what that upper boundary is because of the limited number of the SMQ MACE events. So, I just sort of wanted to make that point. I

mean I guess the deal is you get more events, you take the non- specificity, you try to reach some reassurance and you see what you get.

DR. BURMAN: Thank you. Dr. Proschan.

DR. PROSCHAN: I guess one of the difficult issues is, what the 1.8 is relative to. I mean apparently it seems that sometimes when you compare to an active comparator, it actually comes out better than when you compare it to the placebo and, given that many of the drugs that have already been approved were approved on a basis of HbA1c, it's possible that those drugs also have cardiovascular harms. So showing that it's better than one of the approved drugs might not be saying that much. So does the FDA have a position on what that comparison should be, what that active comparator should be for example?

DR. PARKS: I think it is important to point out that in this program here even though they are - when referred to placebo control, it's actually add-on. So they were standard background therapy. In our guidance, we do not specify what that comparator should be and we are actually very specific in terms of assessment risk as to all comparators as you will hear in the subsequent discussion. It's very difficult to define or state up front what that comparative must be. It has the complexity and I think a lot of the diabetologists and endocrinologists around the room here could speak to that as well as the complexity of the disease will make it very difficult to say that this must be the comparator for which, and overtime to do a long-term study to assess cardiovascular risk, it's also going to be multiple therapies that will eventually be added on to both groups.

DR. BURMAN: Thank you. Dr. Teerlink, did you have another comment?

DR. TEERLINK: Maybe I can, I am just struggling a bit with how to proceed with my thinking and I think may be the FDA can help me figure out about this. In the guidance document, I think it very appropriately suggests that you have to do these in high-risk patients and so you can assess the effect in its cardiovascular events. If we get, I mean it becomes an issue of generalizability. So what kind of guidance can you give us if we believe that the population in which the drug is studied doesn't have relevance to the question of cardiovascular risk? How are we to apply data from this data set to another, to the issue of cardiovascular risk?

DR. PARKS: I guess you're touching on point discussion number one. Something that the panel members need to keep in mind as Dr. Joffe mentioned in his introductory statement is that these are programs that were all ready underway; completed at the time the guidance was finalized. So, knowing that limitation, there is not a whole lot you can do at this point. Going forward, the guidance clearly specifies that there should be an attempt to enroll more patients where you can capture these events and perhaps generalizability to the population will be to prescribe these drugs.

DR. TEERLINK: So are you suggesting that we apply a different standard of protecting the public health against these potential complications for agents that were already in that process or how we are suppose to balance those?

DR. ROSEBRAUGH: Yeah. I don't think we're suggesting that at all, I think what we are asking and we will want you folks to help us with during the discussion part is whether you think having an MI in somebody that has only had diabetes for three or four or five years, is different than an MI in somebody that has had it for 10 or 20 or 30 years. We need your help with that, that's part of the question.

DR. BURMAN: Thank you. Any other questions from the Committee? Please.

DR. FELNER: Yeah. Just because the cardiologists, I think Dr. Alexander from Duke had brought it up, and being a pediatric endocrinologist, I don't see CPK too often or MIs for that matter. Is it safe to say or agreed upon that if you have an elevation in your CPK, but you have no EKG findings, that that is not a cardiac event, is that a -- can you say that?

DR. KONSTAM: No, you can't say that. What you can say is that, I mean there are various ways that MIs are adjudicated, if you really do it up front and care about pre-specifying. One typical approach would be to say that you need two out of three of CPK elevation, ECG abnormality, and clinical symptoms. That's a typical approach, there are others, but you certainly could not say that, with only a CPK, it is not an MI. What you could say is that, as has been discussed and I think well, it's not specific for an MI and there are other things that could cause it.

DR. FELNER: Without clinical symptoms and without EKG findings, an elevated CPK, it means very little, correct?

DR. KONSTAM: Well you just said it a little bit differently, I mean…

DR. FELNER: Well, that was to say, after you made your comment, that was what I want to add on because…

DR. KONSTAM: I wouldn't say it means very little, I would say that it's a concern and it's a possible MI. I don't know, how and where to titrate it. I think the discussion was very good, there are a number of other possible reasons for a CPK and without the other documentation you are left with a great deal of uncertainty.

DR. BURMAN: If I might, one question on that, would getting troponins help, and I don't think they were gotten, but if they had been obtained, they would have been more specific?

DR. KONSTAM: Yeah, definitely, yes.

DR. BURMAN: I assume they weren't obtained?

DR. KONSTAM: Well, these were just AE reports. That's all this is, so this is with no pre-specification.

DR. ALEXANDER: So on one or two of the cases, there were CKMB samples drawn along in response to the elevated CK, but and maybe one troponin I saw, but in the vast majority not, and I just asked the BMS folks. They don't have a blood bank because that would be another way of going back and checking, but these were elevated total CPKs, the vast majority of which didn't have other cardiac markers.

DR. KONSTAM: While you are still up there I mean, may be you could help us because I mean, I guess, fair enough, I mean, I agree with everything you said, but I guess it sort of comes down to why are we even looking at this analysis and I guess we are looking at this analysis because there are so few narrower MACE events. So we are looking at this analysis I think, and maybe other people can comment, to get greater confidence in what the actual upper boundary might be and I guess when I look at that drift accepting the non-specificity, it doesn't help, right? I guess that's the way I am looking at this.

DR. ALEXANDER: I mean, the way, again I got involved in this about a month ago and wasn't involved in the previous discussions with the FDA guidance. My perspective is that the point estimate for SMQ MACE shifts toward one and, if you look at only the CPK elevations, it's right on one, and if you add a lot of non-specificity, that's

what you would expect. I agree with all of the comments that we have heard about the relatively low risk and small numbers of events in the population making it difficult to be certain that there is not an excess risk.

DR. MELE: Can I just point out one thing about the CPKs, that most of these CPKs, these patients did not discontinue. So they continue on the trial.

DR. KONSTAM: That's not surprising; I don't find it that surprising.

DR. MELE: I mean, no other event is recorded for them, is what I am saying.

DR. KONSTAM: Right, but I am not sure, if I thought a patient had a small MI for sure, let's say I was convinced the patient did in fact have an MI, I am not sure I would discontinue the patient either from the study. In other words, the fact, I am not sure how well that speaks to whether the clinician really thought or whether this really was an MI the fact that it was discontinued, because I don't think that there was a high level of concern by the investigators that the experimental drug was likely to cause MIs. So I am not sure they would discontinue, I don't know how much that helps me.

DR. TEERLINK: You probably would have admitted them, you probably would have admitted the patient, these are mostly out patient.

DR. KONSTAM: I think we're on the same wavelength, this is a very non-specific finding, I agree with that, I just I don't, you know.

DR. BURMAN: Well, why don't we move on? Thank you very much. I think Dr. Teerlink, did you have a comment before - a question. Please identify yourself for the record when you speak. Dr. Savage.

DR. SAVAGE: I guess, I'm sort of trying to put in perspective the problem we are facing here. If you really want to look at the effect of a new drug, you

would like to use it as monotherapy in patients where you wouldn't have the problem of having all sorts of other drugs, but given the recommendations for the level of glucose control that are now in place, that by it's very nature is likely to mean you are going to have relatively recent onset or mild fairly stable non-progressive diabetic patients who are going to have a relatively low risk of having cardiovascular events, and particularly with the aggressive - with the advocacy of aggressive lipid lowering and blood pressure control and so forth, the situation has gotten progressively worse as far as evaluating the risk of a new drug.

So, one of the things that I think would be helpful for us to see if we have a presentation like this is some sort of a graphic that indicates the - I don't know whether it would be risk or, something about how representative, the group of patients that have been studied are, as compared to the general diabetic population. In this case, I think from what I have read and heard, it's a relatively low-risk group of people and that's why we are struggling with all these nuances of trying to extract extra information out of things like the CPK.

DR. BURMAN: Thank you. Dr. Wyne, did you have a question?

DR. WYNE: I was just trying to put Eric's question back into clinical perspective about the CK. When you monitor CK routinely in the study visits, that is not looking for cardiac ischemia. That's looking for Rhabdomyolysis really. So it's not, they are just doing it routinely and you have to look at it the context of the individual's baseline, for example an African-American is going to have a higher baseline. anybody who is on a Statin is going to have a higher CK at those study visits, which is why Statin use becomes very relevant. We have to remember that we don't use CKs drug for myocardial ischemia anymore because they are not sensitive enough. That's why we

developed the troponin ANSAID. So what I am trying to say is the answer to your question is, we would look at that elevation and not even think myocardial ischemia in routine clinical practice nowadays.

DR. BURMAN: Any other comments? Dr. Veltri, you had a comment?

DR. VELTRI: I was commenting on the diagnose of MI, but I think others have told or have mentioned that very nicely, symptoms, EKG changes and/or MB positivity or troponin positivity. If we are talking about other events and I think the guidance allows for other events besides CV death, MI and stroke, and that is really a recurrent myocardial ischemia or new myocardial ischemia leading to revascularization where perhaps a CPK MB or troponin periprocedural may show myonecrosis.

So in order to perhaps maybe improve upon the events, we have excluded revascularization events in a setting of a hospitalization recurrent ischemia. Perhaps that can tease out, I don't know what the incidence of revascularization in the database was. The other observation would be we are looking at only first events. Obviously there are other events that occur if the first event was non-fatal such as an MI, then a stroke, then a CV death. So there is other ways of potentially enriching for events by looking at other events or secondary or tertiary events.

DR. BURMAN: Does either the FDA or the Sponsor have a comment regarding that especially the issue of revascularization?

DR. WOLF: Before we submitted the NDA, our primary assessment of cardiovascular safety at that point in time was our endpoints of acute CV events and that event included revascularization procedures and you recall that we had 41 cases of primary MACE on our data seg. We had approximately 60 cases of acute CV events.

When we analyze acute CV events, we qualitatively arrived essentially at the same answer.

DR. BURMAN: Thank you. We have a few minutes left before lunch. Does anybody from the committee have another question?

DR. FLEGAL: Yes. I'm trying to understand how this discussion fits into the guidance. The guidance talks about new therapies which have to go through or are recommended to prospectively adjudicate events and include patients at increased risk and so on. So that's new therapies in the future and then there is some other assessment that is going to be discussed that's already approved treatments. Are we - is this a third category we are talking about here of a therapy that isn't really new and isn't really already approved and if this were to be approved would it then go - would this be considered just to be approved to have already completed some kind of cardiovascular safety assessment as opposed to already approved therapies that haven't or how would these three categories fit in together, that's my question.

DR. PARKS: I think that it's important for the Committee to understand that when the guidance was published in December, it was also decided that this requirement to assess cardiovascular risk with this picture again I say the goalpost as Dr. Joffe had referred to before, 1.8 and 1.3 was important to apply for any therapy, any NDA that comes before the FDA, including the ones in house. So, with that, that's what's going to be uniform across the board for all these programs. What becomes more complicated are the companies who have been caught in the middle. While this - the line has been drawn in the sand and they stood before that line. It's not just the recommendations that you provide to us today based on the quality of these data to meet that goalpost, is not only for these applications here but it will also help us because there

are other programs who had already initiated phase 2, phase 2I are very much well under way.

We recognize that that is a difficult task before you, but if there is an understanding that glycemia control is important, these therapies have a benefit with respect to controlling diabetes, now the next question is, if that has been established for us, and I know that is not on the table to discuss here, is that whether or not the quality of the data that they have here will address that cardiovascular risk goalpost?

DR. BURMAN: Thank you. Dr. Levitsky.

DR. LEVITSKY: So as a pediatric endocrinologist, once again I can assure you that I have used say the glitizones and I have never seen anybody have a heart attack or an adverse cardiac event, which of course is exactly what we are addressing here today. So what are the options for a drug, which obviously does something for blood sugar, and in which you cannot define an adverse cardiac event, and yet you may not have enough data to define it? What are the options in terms of the FDAs dealing with this drug? I am not sure I quite hear that.

DR. ROSEBRAUGH: So, let me just kind of take us back and at least give my recollection of the advice we heard about evaluating cardiovascular risk. I am going to qualify that by saying when it's my recollection, I remember quite clearly everything I did in high school. I remember everything I have done in the last fifteen minutes but everything in between is sort of a blur to me. So there may be others that were at that meeting that have a little different impression but I will give you my impression. So what the committee was trying to do is to say, we need to have some sort of balance where we at least know we have some comfort that there won't be a cataclysmic MI result from a drug. Recognizing that to get definitive data would take

anywhere from five to seven years on top of that which could delay drugs getting out on the market. So they sort of had a two-stage approach.

They said let's try to get enough events or at least see enough events so that we know that there is a balance such that this drug will not create a great risk, and if we see that then they can be approved for marketing and at that point we can do a big long outcome study and get definitive evidence. So that's kind of where we are at with this drug is to say okay, have they hit that first stage or where we can say, you know, we don't see something cataclysmic here, we can let them on the market until they do their big long outcome study or, you know, one of our questions is even well, you know, they are under 1.3, what do you all think of that. So that is sort of what we need help from you all.

DR. BURMAN: Thank you. Dr. Konstam.

DR. KONSTAM: Yeah, can I ask - let me give you my - the way I am thinking about this and ask you if it's right or not okay. I mean and I was at that last panel too. So, I mean, as you say, I mean there was an attempt to sort of drive us to say that at the time that something comes to market there is a certain bar, there is a certain level of confidence that we would like to have that it does not cause cardiovascular harm. That bar might be high enough that you're done or it might be at a level that it's approvable but more studies are needed and those were the two bars. So the guidance document that you generated really was in the spirit of that.

It defined these two upper boundaries and it not only that, but it defined really how you got there. So, the type of populations that you have to study and the approach to pre-specification and adjudication, all is there that got you to those levels of confidence. So now we are sort of in between with an NDA that came along prior to that

document being issued. So I guess the way I am formulating this is the question to the panel is okay, with the data that we have in the way we have analyzed it, despite the fact that the guidance document was not specifically followed, does the panel feel like we still have that level of confidence that was expected without having specifically followed the directive of the guidance document, is that sort of the way you would put the question?

DR. ROSEBRAUGH: Yeah. I think the others can weigh in. I think you nailed it exactly, the other thing I should point out too is that people need to understand the guidance document does not mean you have to do it; it just means this is the guidance we recommend that you follow to make us happy.

DR. BURMAN: That's always a good thing. Any other comments or questions we have, Dr. Levitsky.

DR. LEVITSKY: What will the FDA's role be in planning this future long-term study that will evaluate cardiac risk, which seems very ill defined right now, well meaning but ill defined?

DR. ROSEBRAUGH: Well, it's, let me just tell you, it kind of depends on some of the advice we get and what we determine when we get together and talk internally about it. We now have new authorities such that if we determine that this was a safety issue that we had to have information on, it would be a post marketing requirement and under a post marketing requirement, we have great influence on exactly how the study will be run and we have to sign off on this, we have a lot of influence.

DR. BURMAN: Thank you. Does the Sponsor have a comment?

DR. DANIELS: Dr. Daniels just following up on that last comment. We have a great desire to do the appropriate large outcome study after approval if possible. I

think the issue is that the study design is actually relatively unformed because we want to make sure we can have the right discussions with both the FDA and other regulatory agencies who are interested in this question.

So in essence, the lack of certainty of our design reflects not a lack of commitment but a desire to be in active dialogue with regulators and I think also academic groups that prudentially want also to have some input into the design of the study as well. So, I just want to make sure I can covey that as a sort of the senior medical authority for BMS and I think in consultation also with our AstraZeneca colleagues that the commitment is there, it's real. It seems maybe a little bit unformed, but it's unformed I think because we really want to have the right discussions both with the FDA, other regulatory authorities and academic groups as to how best to continue to develop the cardiovascular profile and other meaningful outcomes for Saxagliptin. Thank you.

DR. BURMAN: Thank you. I think if it's all right, Paul and I were talking and if it's okay with the rest of the FDA, we have a few minutes before noon and would it be okay to open up questions not only for the FDA but for the Sponsor as well, is that okay? Does anybody on the committee have any additional questions on any of the presentations this morning? John?

DR. TEERLINK: I was just wondering if they have had a chance to do any of the analyses that we had asked for in terms of showing distribution in terms of the stages of Coronary Kidney Disease, in terms of distribution along those lines and the other extra things that I had requested before. I know we can wait till perhaps after lunch if you need the extra time, but I do want to see those.

DR. WOLF: Could we have the slide on use of Statins by treatment group? Please project slide 3-58. This slide describes the use of Statins based upon

whether they were based on a hypercholesterolemia or not. Approximately half of the patients we had based on hypercholesterolemia were on a Statin.

DR. TEERLINK: That's very helpful. My question was in regards to the stages of chronic kidney disease that patients had in enrollment before at baseline.

DR. WOLF: Let me first share some data with you, we were asked also about the number of patients who had baseline Diabetic Kidney Disease. If I could please project slide 3-52, so this slide summarizes the prevalence of micro-vascular complications of type 2 diabetes in our population. I think we may need to comeback to you after the break on the breakdown by severity of renal impairment. The vast majority of the patients who had an abnormal creatinine clearance were between 50 and 80. So they fall into the mild category. I do want to remind the committee that we have an on going clinical trial, randomized clinical trial examining patients who have both moderate and severe renal impairment.

DR. BURMAN: Thank you. I had a question for the Sponsor as well. Two quick questions, number one, do you have any further information on tumors of the skin either in animals or humans, you talked about ulcerations a little bit, and any more information on pancreatitis whether it's acute or chronic or silent with elevation of pancreatic enzymes either in animal or human?

DR. WOLF: We did not see evidence for pancreatic injury in our non clinical safety studies, and I will now ask Dr. Roland Chen to come to the podium to describe our clinical experience in pancreatitis and the clinical development program.

DR. CHEN: Events of pancreatitis seeing in the Saxagliptin clinical program were frequent and balanced between the treatment groups. Can I have slide 27-1 please. This slide summarizes the adverse events of pancreatitis in our phase 2b3 pool

population. There were six cases of pancreatitis in patients who received Saxagliptin versus two in the control group. The results are shown for the various Saxagliptin doses, all Saxagliptin comparator with the specific cases represented in the left hand column. Of the six cases that we are seeing in patients who receive Saxagliptin, two cases were considered serious.

One of the two cases, who received control, was considered serious, that is serious adverse events. Five of the six patients who received Saxagliptin and had an event of pancreatitis, the past medical history either included a risk factor for pancreatitis or a previous history of pancreatitis. There is one case that had no risk factors, the case that was deemed to be of moderate intensity and not related by the investigator. In this subject, the patient also had concomitant AEs of gastritis and duodenitis in the same episode. This patient continued on therapy without interruption and this case resolved after 47 days while continuing on Saxagliptin.

DR. BURMAN: You don't think very much - you don't have data regarding measurement periodically of amylase or lipase in any of these patients?

DR. CHEN: We did not routinely collect amylase or lipase in the program.

DR. BURMAN: Thank you. I think we have one last question before lunch.

DR. KONSTAM: Well, the problem with having more time is you start thinking of more things to worry about. So in that spirit, so the business about the lymphocytes, I guess I am really unsure whether to worry about it or not or how much to be worried about it, and I am also not sure how reassured I am about counting the number of infections because I don't think there were that many in the control group. So I

wonder if the Sponsor could comment anymore about it, where you are on this in terms of assuming approval. What post marketing recommendations, follow ups, screening are you going to propose?

DR. WOLF: As part of our pharmacoepidemiologic program, we are going to be including assessments of serious infections to look for any complications that might be related to the potential immune effect, which we have not seen in our clinical development program to date. Of course, our randomized trial experience, including our large randomized trial that provided an additional opportunity to look for that sort of an issue.

DR. KONSTAM: You will specifically be looking for that perceptively in whatever large randomized trials you conduct going forward?

DR. WOLF: Yes. I mean, we will continue to monitor the lymphocyte effect that we did see.

DR. KONSTAM: Infections?

DR. WOLF: Infections, yes.

DR. BURMAN: Good. Thank you all. Any final questions before lunch or comments?

(No response.)

Thank you all for the discussion. Does the FDA have any comments or questions?

(No response.)

Well, we will break now for lunch until one o'clock. We will reconvene in approximately one hour. Please take any personal belongings with you. The ballroom will be secured.

(Lunch recess.)

OPEN PUBLIC HEARING SESSION

DR. BURMAN: Good afternoon. We are now going to proceed to the beginning of the OPH session. As an announcement, both the FDA and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing Session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the Sponsor, its product, and if known, its direct competitors.

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

The FDA and the committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this Open Public Hearing to be conducted in a fair and open manner where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the Chair. Thank you for your cooperation.

This afternoon we have one speaker for the Open Public Hearing session, Kelly Close, who is editor-in-chief of diaTribe. Ms. Close.

DR. CLOSE: Thank you. Good afternoon Mr. Chairman and members of the committee and interested members of the public. I am Kelly Close and I have had type I diabetes since 1986. Thank you for the opportunity to comment.

I am editor-in-chief of three publications about diabetes and obesity. DiaTribe is a newsletter for patients about new products and research to treat the disease. Closer Look is a newsletter about products and research for people who work in the field. Diabetes Close Up synthesizes developments in the field and interviews notable scientists, doctors and diabetes educators. I began writing about diabetes and obesity full-time in 2002. Over the last few years we have published 14 bi-monthly issues of diaTribe, 89 monthly issues of Diabetes Close Up and over 1,000 close to daily issues of Closer Look. Approximately 15,000 patients with diabetes subscribe to diaTribe.

As disclosure, various manufacturers, doctors, nurses, and researchers subscribe to Closer Look and Diabetes Close Up. These subsidize diaTribe, which is free, and does not take advertising. I have no relationship with either manufacturer bringing today's therapy before the Agency.

On behalf of thousands of diaTribe readers and dozens of writers, I convey my deepest thanks to doctors on the panel for all of your work, and to the patient representative on the panel, Rebecca Killion, who has provided such valuable voice for us. We appreciate FDA's effort to advance its mission by protecting the public health by assuring the safety and efficacy of drugs and to advance public help by helping speed innovations that make medicine more effective, safer and cheaper. So I love your mission.

I have had diabetes since I was a teenager. Most of you are doctors or otherwise close to diabetes and so you know what that means. Here are some of my numbers: I pricked my finger to test my blood glucose about 67,000 times in my life, I have taken over 28,000 injections, I have worked my way through 550 bottles of Insulin, I have been mildly, moderately or severely hypoglycemic about 3,000 times. That's the downside of a good A1c and in interest in avoiding complications like blindness, dialysis, and cardiovascular disease.

I put a pump set, painful, in my abdomen about 1,100 times. I have had the benefit of diabetes education and I know how much I want to avoid long-term microvascular and macrovascular complications. This means sometimes I try hard and become hypoglycemic. As many patients with diabetes feel, I know, my body often betrays me. In all, I have had 24 emergency room visits to treat hypoglycemia in 23 years. I have had an A1c under 7% for as long as the measure has been in place but like many who are ostensibly in good control, the wide range of my glycemic variability is striking.

So I mention this history because I realize that FDA will be making important decisions about how it evaluates new diabetes drugs, specifically whether prospective drugs need to be tested for cardiovascular risk in the absence of pre-clinical or clinical signals of actual or potential risk. So as you can imagine no one has a greater stake in safe drugs than the patients themselves. Right now the burden of good diabetes care is extremely high. I feel that imposing additional regulatory barriers on new drugs in the absence of those clinical or pre-clinical signals may stifle innovation and could set back diabetes care in America. From a patient perspective I must admit that I question

the rationale for the "one-size fits all" cardiovascular risk exclusion standard, again, in the absence of pre-clinical or clinical signals of actual or potential risk.

So let me explain why I think new treatments for people with diabetes are needed. First, as mentioned today earlier by Dr. Wolf and others, we are not achieving our goals as patients with diabetes. Our success rate, if you will, is really low. You might say it's abysmally low. Only about 55% of people with diabetes in the United States are at their glycemic targets and only 7% of patients with diabetes are at their glycemic, lipid and blood pressure targets, 93% of us are outside of that target zone in at least one area. Patients may be able to benefit from better, more tolerable, more convenient and simpler medications.

Second, prevalence is up. Four thousand people with diabetes are diagnosed daily in the US. Eight hundred people have been diagnosed since we have gathered here today, since 8:00 this morning. Diabetes complications are increasing, which in turn is driving costs. 55 people with diabetes go blind daily, 120 more start dialysis, and 230 will require an amputation, just after today. The cost to the quality of life can't be understated. The economic costs are increasing so quickly that they are creating an unimaginable burden on our healthcare system.

In 2006, people with diabetes represented 7% of the population but accounted for 17% if healthcare spending. A significant chunk of this was tied to preventable complications. So we didn't need to be spending that money on diabetes, we didn't need to be spending it at all. According to the most recent data from the American Diabetes Association, between 2002 and 2007 the direct cost of diabetes increased from 92 billion to 116 billion. Many of you have heard these numbers over and over; they are quite often quoted. You know, the real story is really what's behind those numbers. In

that same time period, the cost of diabetes complications doubled from under 20 billion to more than 40 billion. This is in five years. The expectations are that spending on complications will increase to 53 billion in 2012 and 75 billion in 2020 if current obesity trends continue. That's new data from The Lewin Group who made all of the data for the ADA publications on the cost of diabetes in America. Those came out earlier this month.

As everyone here knows, many of these complications are preventable or they can be delayed with improved care, especially care early in diabetes progression, which brings me to my third reason why new treatments are needed. Compliance or adherence to taking medicine is really too low. While not many payers will say so publicly, they indicate privately that adherence to diabetes medications is about 50% and that's on a really good day. This suggests that the armamentarium of diabetes medications could possibly benefit from the addition of better, more tolerable therapies. Notably, today there are no disease modifying alternatives for diabetes available. Perhaps these can be developed one day. That's truly a patient dream. For that to happen, industry and investors must believe in a reasonable regulatory environment. If they don't we all will lose.

Why are A1cs so low? Why is diabetes management so challenging? The answer is undoubtedly a combination of factors, but we believe from many surveys with patients and doctors that it could largely be because current diabetes medications are not broadly tolerable. The most widely used diabetes medication today, for example, Metformin caused GI problems in 40% of patients who took it the international multi-center randomized double-blinded placebo-controlled 44,000 patient DREAM trial. That was reported in 2006.

It is also well known that Sulfonylureas cause weight gain and hypoglycemia. The class is also widely suspected to cause beta cell burnout but given that it is generic it is unlikely, as I understand it, to ever undergo any safety profiling of its own even though it is among the most common medications taken and even though many suspect medicines in this class would never be approved today.

Other classes of widely prescribed diabetes medicines cause weight gain, edema, fractures, and other problems. Insulin has the lowest therapeutic index of virtually any drug on the market and was in 2006 the drug most cited for causing adverse drug events in emergency room visits, frequently due to hypoglycemia or to DKA. It also causes weight gain, which can contribute to heart problems. Obviously, I am very tight with Insulin. I am beyond grateful that it was invented. I am also very much a follower of new Insulins in development and hope that they will, with other drugs, see a reasonable and fair regulatory environment.

Dr. Steven Nissen of the Cleveland Clinic asked at the July 2008 FDA Advisory Panel why people with diabetes needed more drug classes. You know, as a patient I was really surprised and disappointed by this question. While I want all our patients to be as safe as possible, it's important to be concerned about patients who aren't finding success with current treatments. To be satisfied with a range of therapies that has such a gap in treatment success is also surprising and disappointing.

Thank you in advance to the committee for considering new alternatives for all adults with diabetes that will improve diabetes management. Currently we seem largely still in a 'one size fits all' mode of treating diabetes in the US. The system, for the most part, doesn't support physicians, especially primary care physicians, spending a lot of time with patients. So I hope you will encourage making safe, tolerable,

inexpensive therapy alternatives for a patient so they can do more to help themselves so that we can do more to help ourselves.

In case I wasn't clear, let me tie this to the most important issue of our day and underscore that this lack of good diabetes management is an economic issue. It's an economic issue and it's a moral issue. We need new drugs so that people can get earlier and more aggressive treatment that they will take so we can work to prevent and/or delay diabetes complications. Of course even if people achieve better diabetes management we know that diabetes is a progressive disease at present. So we would also, if we were making a list of what patients wanted, say that we would like disease-modifying drugs. This seems unlikely to happen unless we are in a system that encourages innovation. That's what the US is all about and I would hate as a patient to see that stifled.

In closing, my two central messages are: we continue to need alternate options for the treatment of type 2 diabetes and I would like to live in a system in which innovation is encouraged, not discouraged even passively. While I obviously support the objectives, fully support the objectives, of assuring safety of all drugs including for diabetes, I strongly encourage FDA and its advisors not to put excessive barriers in the path of development that will threaten innovation and investment. Please consider this as new drugs come before for you.

Thank you very much for your time. Well-controlled diabetes is the leading cause of nothing, as Dr. Bill Polonsky says of the Behavioural Diabetes Institute. Although we hear a lot these days about prevention of diabetes, I would urge the committee to consider the delay and prevention of complications by considering new alternatives that will help patients, particularly early in the course of the disease. For the patients and families of the 24 million adults with diabetes in the US and for 57 million

people with pre-diabetes, thank you so much for your work on making diabetes easier for patients and for families. Thank you.

DR. BURMAN: Thank you very much. I believe that closes the OPH session and the Open Public Hearing portion of this meeting is now concluded and we will no longer take comments from the audience.

(The Open Public Hearing Session closed.)

QUESTIONS FROM COMMITTEE TO

SPONSOR AND FDA

DR. BURMAN: The committee will now turn its attention to address the task at hand - the careful consideration of the data before the committee as well as the public comments. The format for this afternoon will be as follows: We will ask the Sponsors to come up in a minute to bring us up-to-date on the issues regarding the questions from Dr. Teerlink and the committee this morning regarding chronic renal failure. Then we will open the floor for a period of time for further discussions for the FDA and the Sponsor. Then we will move right on for the committee to discuss the issues at hand in an organized fashion. Would the Sponsor please come up as they requested and we have requested them to bring us up-to-date on chronic renal failure issues?

DR. WOLF: We will respond to that question. There were a few other questions that we wanted to clarify that we worked on during the break. We were asked about signals for a skin cancer either in the non-clinical or the clinical environment. We have performed two long-term non-clinical carcinogenicity studies, in those studies, and they performed at high multiples of the clinical exposure. We saw no signals for increase in cancers including skin cancer of those non-clinical trials. During the break we looked

at the experience with skin cancers in the clinic and again we saw no evidence for a signal for increase in skin cancers among Saxagliptin-exposed patients.

There was a comment during the morning proceedings about whether we have long-term duration experience in our clinical program. If I could have the slide that shows the experience, please project slide 3-51. This slide summarizes the experience in our phase 2b/phase 3 program for patients who had at least five years' or ten years' duration of type 2 diabetes. Please note that approximately 20-30% and in some cases 40% of patients had at least five years of disease. You see the experience for at least ten years. This slide also displays the experience for creatinine clearance below 80. I know that you asked for greater detail and that's what we are going to provide to you now. Dr. Chen...

DR. CHEN: Could I have slide 2-101 please. This slide summarizes the baseline creatinine clearance at baseline for our phase 2/phase 3 pool population. Data are shown for the various Saxagliptin doses, all Saxagliptin in control. We have broken this out into creatinine clearance of less than 50. We have cut the 50-80 range into two categories - that is 50-65 milliliters per minute, 65-80, and greater than 80. As Dr. Wolf mentioned earlier, the majority of patients had a creatinine clearance that was greater than 80 at baseline. About 16% of those patients had creatinine clearances between 50 and 80.

About 1 to 1.5%, a small minority, had creatinine clearances of less than 50. This distribution was largely a consequence of our broad use of Metformin in our clinical program and the Metformin package label, which actually contra-indicates patients who have serum creatinines of greater than 1.5 or 1.4, depending on gender. As Dr. Wolf mentioned earlier we are conducting a renal study in patients with moderate, severe, or end-stage renal disease to gain more experience in this patient population.

DR. BURMAN: Thank you very much. Does anyone on the committee have a specific question on those several slides? Thank you for doing that so rapidly. I would now like to maybe give you an overview. We will have, as long as it takes, usually 20 maybe perhaps 20-30 minutes, of questions for the FDA and the Sponsor if there are any. When that is done, we will then move to discuss each question of the four questions; we will spend about a half an hour on each question. Depending on time, we would like to end that session around 4:00 or sooner, we then want to have an hour left aside if needed for the specific voting questions. Any questions on the agenda?

(No response.)

Then let me open the floor up for any further discussions or questions or comments by the committee to the FDA or the Sponsor. John?

DR. TEERLINK: So just to clarify my earlier question about the duration of diabetes, what I was actually looking for was a sub-group analysis of the patient's event rates looking only at those who had diabetes for ten years or longer, since that is actually going to be the bulk of the patients who will, in the real world, be receiving this. You know, if we are going to be trying to look at that group, I think it would be useful to look what happened to cardiovascular events in the patients who had diabetes of at least ten years' duration. Unfortunately that's only 10% of the patient population but it is, you know, it is what it is. So that's what I actually had been interested in saying.

DR. BURMAN: Thank you. Anybody else on the committee have any questions? The Sponsor wanted to make a comment? Please.

DR. WOLF: I'm sorry I didn't fully appreciate the question you were asking, but we do have an analysis at least for patients who have at least five years of disease. You are not interested? Okay.

DR. TEERLINK: No, because I mean the cardiovascular events, you know, this is in the diabetes literature, the risk begins actually increasing at the ten-year point. It's continuous but it goes up more then. So if you have it for the ten-year, I would love to see that.

DR. WYNE: Can I clarify? What he is asking is, of those 40 events, what's the duration of disease in those people? Is it possible to see a breakdown with those 40 events? What we want to know is, Are those events enriched in people who have longer duration of disease? He is specifically using ten years as a break point because that's what the recent studies seem to indicate. Where I am disagreeing with him is I think it's a continuum where that increase in risk definitely picks up after five years, probably around seven, but absolutely beyond ten years. So that's what he is wondering. Is it possible those events are all in people of more than ten years or is it evenly split?

DR. WOLF: I'm sorry. I don't know the answer to that question.

DR. BURMAN: Thank you. Any other comments or questions by the Committee? Yes, Dr. Lesar.

DR. LESAR: Yes there was a discussion related to how many patients were on Statins but I am also curious if there was balance and some measurement of other medications that might alter rates of cardiovascular events, either positive or negative, such as Aspirin, Beta blockers, nonsteroidal anti-inflammatory drugs?

DR. BURMAN: Does the Sponsor want to respond to that?

DR. WOLF: Could you repeat?

DR. BURMAN: Sure. Please repeat the question.

DR. LESAR: Sure, my question has to do with the use of concurrent medications that might alter the frequency of cardiovascular events outside of Statins,

which had been discussed. I am particularly interested in things like potentially chronic Non-steroidal anti-inflammatory use, which may obviously increase, or such things as, what was the percent of patients in groups that took Aspirin, Beta blockers, ACE inhibitors, etc. that might alter cardiovascular events rates.

DR. WOLF: Could you please project slide 3-99. The frequency of ACE inhibitor use, angiotensin receptor blocker use, beta-blockers, and calcium channel blocker is presented on this slide. We, at the present time, don't have information on nonsteroidals but we can address the questions about ACE inhibitors and beta-blockers.

DR. BURMAN: Thank you. Does anybody have any specific questions on that slide? Let me open further any comments by the committee to the FDA or the Sponsor before we move on to discussion of the specific questions.

(No response.)

Seeing none, then we shall move on.

DISCUSSION AND QUESTIONS

TO THE COMMITTEE

DR. BURMAN: We will now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel. In terms of overall agenda it's approximately 1:30, that will give us 30-35 minutes or so for each of the four questions and I know that there is some overlap between each of the questions. Then we will end that and then go to specific discussion of the voting issues and then vote. Let me read the first questions and open it up for discussion.

Question No. 1:

Please discuss whether the low cardiovascular event rate in the Saxagliptin clinical trials permits a reliable assessment of cardiovascular safety. We have had some discussion of this but I would like to open it up for further clarification and discussion.

DR. PROSCHAN: Yeah. You know, as mentioned earlier about, you know, there aren't that many events and there are a lot of different analyses done. That I see is actually an advantage. The first one is not an advantage; not having too many events is not an advantage. Analyzing it in many different ways is an advantage and I think it showed that the results don't change very much as you change your methodology, which is important. Of course, you know, it's true that there are not a lot of events. In particular, that causes problems, you know, when you are looking at the more specific cardiovascular outcome because some trials have no events and, you know, how do you include them? I mean the traditional method of analyzing that kind of data when you have a small number of events is too conditioned on the total number of events you have in a given trial.

Say, okay, given that we have had five of these events, what's the probability that they would be as lopsided as they are, in terms of treatment - the control versus the treatment? If you do that type of analysis the natural thing to use is the odds ratio. It just so happens that when you look at the distribution of that kind of statistic, what comes out naturally is that it depends on the odds ratio. Here we have relatively small event rates so the odds ratio and the relative risk are about the same thing. So, you know, I found it reassuring that the different analyses came out with similar conclusions by and large.

DR. BURMAN: Thank you. Dr. Konstam?

DR. KONSTAM: Yeah. You know, I think there is a really key point that needs to come out from this question because in listening to the questions and comments around the table, I think it is important. Because I think there are two different issues here; one is how many events do we have? When we have a low number of events, what degree of confidence can we build, you know, about the point estimate in the various boundaries. So that's a purely statistical question and a critical one.

The other question is a population related question; Is there a reason to expect that the hazard or odds ratio will be different in different populations? Is there a reason to expect that in this population that is a somewhat lower risk, although I would challenge that it's really a truly low risk population, but certainly a lower risk population than one that was enriched with a lot of non-cardiovascular disease. I guess it becomes a biologic question. Will those two different populations differ in their response to the drug or in the impact that the drug has on cardiovascular safety?

So I think it's, in our discussion and deliberations, really important that we separate those two out. The first one we can deal with, you know, just by looking at the statistics as best we can and getting our own estimate of it. I think it really helps me that the point estimate, a lot of the point estimates, is to the better side of unity. So that's something that I think will come out. The other issues we can't deal with, although I must sort of challenge myself to ask, you know, do I know of another drug that has two directional effects that actually drives the point estimates in a good direction in a low risk population and a bad direction in a high risk population?

Now I don't know of such a drug, I can't think of one. I think that is another issue. I think when you are going to expose these drugs, you know, to patients who have high cardiovascular risk, as others have pointed out, as John has pointed out, I

guess it's worth knowing I guess at least, you know, it's worth asking, will it have a different effect in that different risk population?

DR. BURMAN: Can I ask, you had mentioned that you don't know of any drugs where there is a lower risk in one population and a higher risk in a high population. What about no risk, no statistically significant risk or signals in the low risk population?

DR. KONSTAM: I don't actually. Here, again, we will come back because here we have point estimates that are actually in a good direction. So it's sort of reasonable to ask the question that way. Asking the question even the way you did, I must say and, you know I would ask others on the panel, I am not aware of a drug that we know the risk only emerges in a high risk population. That's to say assuming that you really knew what the risk was in the lower risk population. The problem being, do you have enough events to count? That's the critical thing. If you had enough events to count and you knew that it was no risk in a low risk population but the risk emerges in a high-risk population, I am not aware of that.

DR. BURMAN: Thank you. Other comments? Dr. Veltri.

DR. VELTRI: I agree with Marvin on this one. I think what is also maybe somewhat reassuring is the fact that there aren't either any pre-clinical signals or at least it doesn't look like there is any off target issues there, which should be the same in both the lower risk, intermediate risk and higher risk patient populations. So barring, I mean there may be some unknown off target effect here, but the biology would suggest and what the Sponsor has shown is that there really isn't any other pre-clinical signal that would suggest that there would be a differential effect in perhaps the higher risk population. I don't know of any example that you are looking.

DR. BURMAN: Ms. Killion.

DR. KILLION: Thank you. I wanted to step back from a patient point of view and take a sort of a 30,000-foot look at this. When I looked at question number one I really thought that it sort of got to the heart of the matter, no pun intended with that. Because, for me, it was one of relevance and when I was trying to dissect this and get away from torturing myself with very daunting statistics, I started looking at this low event rate and said, so what does that mean?

Why is there a low event rate? When I looked at it and I looked at the patient population it sort of came to me today when I was looking at the characteristics of the patient population that was in this study average age, and correct me if I am wrong on any of this, the average age was about early 50s and with a relatively recent onset of type 2 diabetes. As John Teerlink pointed out, the cardiovascular risks are much more pronounced in populations that are 65 and older and have had diabetes for ten years or more, certainly longer than the peak patients in this population had, in the study.

So you are looking at, you know, for whom is this cardiovascular risk assessment most relevant and it's for those older patients, it's for those ones who have these events who were not represented highly in this particular study. So, you know, going back to prior concerns that I voiced, I look at this idea of setting a cardiovascular risk hurdle for new drugs may place a burden on those diabetics who don't fit into those parameters; the ones who develop type 2 diabetes, as we know it, at an increasingly younger age. When I was first diagnosed, they first thought I was a type 2 diabetic and they said, "Well that's strange because it's usually old, sedentary, obese people." I was 38 and I was training for a marathon and I just didn't fit in that. It turned out eventually I was type 1 but they looked at me as a type 2 at first.

So what are our populations? What's our definition of a diabetic? This 'one size fits all' is a little disadvantaging a certain increasing population of diabetics who are younger at onset and face many, many years of treatment. They face these increased cardiovascular risks because of their diagnosis. If you are developing diabetes at 35 instead of 55, you are going to have a good 20 years of treatment ahead of you before you really start to focus on the cumulative effect of your diagnosis, your treatment, your ability to control your diabetes.

So, cardiovascular risk is very important because we know the part that it plays in morbidity for diabetics. We don't want to burden an increasing population who may not have access to drugs, you know, or have delayed access to treatments because we are overly focused on this risk. When I looked at this question and I thought, 'okay, we have this low event rate, that's one question'.

We have this gap period where we are trying to fit this study into, you know, something that was a submission before the guidelines were in place. How do we look at it? I was overall very sanguine about this particular treatment but I wanted to point out that we are talking about lots of diabetics with lots of different needs, with lots of risks that they have to assess. I am not sure where I am wondering off to there but I just wanted to bring that back up to the panel. Thanks.

DR. BURMAN: Thank you. I agree with your points and thank you for bringing them up. Diabetes is a complex disease and for purposes of discussion we divided into the Type 1 and Type 2 but obviously it's much more complex than that. John, did you have a comment as well?

DR. TEERLINK: So partly in response to Mark's comments, in direct discussion of the question, I think the data that's been presented does give us some good

insight into the cardiovascular risk of this agent in the patient population that was studied. I am actually, you know, so that I do believe we have some idea around that. The problem is, there actually is a whole series of drugs. We could go on forever talking about them. That actually depends upon the substrate of the patient population.

Two of them, for example, are the type 1C antiarrhythmics, which are used quite effectively in atrial fibrillation. I don't think we would use them in a patient's post myocardial infarction or with severe coronary disease, because, well we will talk about that. I think that is a reasonable example. There are multiple examples of drugs where we modify how we give them and who we give them to based upon the patient substrate and what their risk factors are at that time.

I am actually feeling quite comfortable giving this drug to a patient who doesn't have underlying significant cardiac risk factors and cardiac disease. I just have no idea what happens when you give this to someone who actually has coronary disease, who has had diabetes for a longer time and actually has these underlying risk factors. They tend to predispose someone to actually having myocardial infarction. If you don't have a coronary artery disease, unless you have actually a prothrombotic effect, you don't usually cause myocardial infarctions. You have to have an underlying substrate and that substrate takes time; so yes.

DR. KONSTAM: So first of all, I mean when you are talking about the type 1C antiarrhythmics I think it's an interesting example. I assume you are talking about the risk of Torsade and sudden cardiac death with those agents.

DR. TEERLINK: Well, in the CAS trial, where you--

DR. KONSTAM: Okay. We have to distinguish between, and I think this gets to Rebecca's point as well. You have to distinguish between relative risk and

absolute risk. Okay. So the absolute risk in a non-ischemic heart disease population from these drugs is small but as far as I know, the relative risk is the same. That there is an increased relative risk, it's not true. Well, how do you know it is not true? I think it is true.

DR. TEERLINK: I think it's not.

DR. KONSTAM: Do you have evidence that it actually - do you have enough evidence? I mean I am not sure how we know that.

DR. BURMAN: This issue is a little off point.

DR. KONSTAM: Well, but I think where it is on point is the question of... So I think we agree that we have a certain body of evidence that's applicable to this population. I guess the question at hand is, what level of concern might we have for a different population? That is, a population for example with established coronary disease. The truth of the matter is that we don't have the exposure but I guess I am sort of throwing back, Do we have the reason to believe that the relative risk would go in one direction in this population and in another direction in that population?

DR. TEERLINK: I tried to address that by suggesting that it's hard to have coronary events if you don't in fact have underlying coronary disease.

DR. BURMAN: Thank you. Are there any other comments please? Dr. Savage.

DR. SAVAGE: I agree with several of the comments Marvin has made and so forth, but I think that - and I feel reasonably reassured from the data that I have seen, certainly for the patients that were in the studies, but at least I don't have a particular reason to be concerned about some of the others. Although, theoretically that's possible. I think one of things that we have learned from the publication of several large

studies in the past year is that cardiovascular complications of diabetes are probably more complex than we had previously thought.

There are a variety of things that can increase risk at various stages of the disease. The progression of diabetes itself with its complication, say the development of autonomic neuropathy, probably increases the risk. The use of complex medical regimens with multiple drugs that have not been fully studied in the circumstances in which they are used, there may very well be some drug interactions that we don't understand.

So it isn't reasonable to try and cover all of these things before a drug gets initially discussed and considered for approval, but it is important to make sure we have in place a follow-up system that if something starts to show up in one of these groups that has not been adequately studied, we will find the signal early rather than 10 years from now when someone writes a paper like was written about one of the other drug classes a few years ago that caused a big furor as to what's being going on for the last 10 years, the answer to which we are still are not entirely sure.

DR. BURMAN: Yes, Dr. Parks.

DR. PARKS: I actually wanted to ask Dr. Teerlink a question. When you mentioned earlier that if they don't have already established cardiovascular disease, I am probably paraphrasing this wrong, their risk of having a coronary event is low. Can you comment on why then several major scientific organizations actually view diabetes as already a CHD risk? My memory is failing here, if anybody on the panel remembers the Statin trial of CARDS, which was in type 2 diabetics, was that a primary prevention population? I think it was. I could be wrong. If it was a primary prevention population, that is actually a patient population of diabetes where they don't already have established

cardiovascular disease, so they haven't declared themselves clinically, but the trial itself certainly showed that they were at high risk for events.

DR. TEERLINK: That trial purposely tried to enroll patients who were at higher events. I would love to - you should compare the event rate, which I don't remember off the top of my head, but I would be happy to compare the event rate from CARDS to the event rate we are seeing here, which is 5 myocardial infractions out of a 4,000-patient trial where supposedly they are at high risk for myocardial infractions, which is not the case. What was the first?

DR. PARKS: Your comments or your thoughts on diabetes already being observed or established as a cardiovascular or CHD risk equivalent.

DR. TEERLINK: It absolutely is. I think that's why we are here. That's why we have such need. I think Ms. Close did a great job of describing why it's important for us to consider, why it's important to take care of diabetes early on. I am still trying to figure out the relationship between actual macrovascular events and diabetes control. I think there are a number of studies and we have been looking at that. That's still an issue. Just because diabetes is a risk factor for a later development of these, it doesn't mean that the administration of a drug in the context of coronary artery diseases is safe.

If you want to call this a high-risk population that's fine; we, fortunately, have a placebo group in these trials. You can look at the placebo event rate. The placebo event rate is lower than most hypertension studies. I mean so, you know, it - yes, these patients will have a lot of events if we follow them for 10 years. These are not the kind of patients that will have a lot of events in six months or a year and all we have to do is

look at the placebo group event rate and we can see that. Does that answer the question? No?

DR. BURMAN: Good. I think Dr. Wyne had a question first, Dr. Levitsky, and then we will go to you. I think Dr. Wyne, did you have a question first?

DR. WYNE: Yeah. I actually had a couple of comments on this subject but on this recent issue of the CHD risk equivalent, I would remind you that the American Diabetes Association took a more moderate approach and from what American Heart or NHLBI has said, and they said that this optional target of 70 is only if you have diabetes and some other risk factors or clinical evidence of CV disease. So if I have a newly diagnosed person who has no complications, normal EKG, you know, everything, I don't necessarily have to shoot for 70 in that person.

In the original data suggesting diabetes as a CHD risk equivalent is actually not very good data. It's Finnish data, it's not American data. So the strength of that statement is actually somewhat to be challenged, I would say. Do I believe everybody with diabetes has coronary disease? Well if I believe the whole population in the world does, yes, but I would argue that I do have some newly diagnosed patients who maybe don't need it and I have some people with Type 1 who probably don't need therapy either.

In terms of the other issue and whether or not these low event rates give us a reliable assessment, when you asked that question of, do we have an example of where a drug may be at risk in a high risk population but not low risk? One thing I was thinking about, I mean this is why we are here talking about this, because we haven't been able to figure out how to predict cardiovascular disease in diabetes. If we go back to what

started this 30 years ago, it is the UGDP and the UKPDS. In one group, a small group, a Sulfonylurea was associated with cardiovascular events.

So we set up a study, the UKPDS which, among other things, was supposed to answer that question. The problem is, is in the newly diagnosed population, which is what the UKPDS was, the CV event rate was so low it took them 25 years to reach significance and even then it was only microvascular. So you do have an example where you have people like the ACORD trial who have events, but the UKPDS who don't have events and we still don't have an answer on whether Sulfonylureas kill people. Can he jump in now, if he wants?

DR. BURMAN: If you're done.

DR. WYNE: No, I'm not done.

DR. BURMAN: Okay. Please.

DR. WYNE: I think the problem comes in, as we want to do the simple study and isolate the effects of a single drug, isolating the effect of the single drug is not clinical reality because we really need to know does it make a difference in the context of usual care? So, for example, in the VADT they mandated blood pressure and lipid control and then ask the question of what does glucose control do? So I think like Dr. Teerlink keeps saying that, not seeing an increase of events in this young, early diagnosis, low risk group can be reassuring but because you don't have a high risk group, you don't know if it truly makes a difference. The analogy there would be the original lipid studies.

They were done in the population with FH because those are the people who had the events and the idea is if we could study a small population with a very high risk we could then go on and do our 10,000 to 20,000 person study. All we have the answer to is that we don't have an increase in risk in the low risk population, which is

important, but it doesn't represent the population of people with diabetes that were going to be treated, whether in this country or in other countries.

DR. BURMAN: I would go to Konstam first.

DR. KONSTAM: Let me just respond to Kathleen because, respectfully, I think we are talking about two different things, okay? I think everybody will agree that in these studies we need a certain number of events to get any kind of confidence about what the drug is doing in cardiovascular events. So, you know, we have declared that cardiovascular safety is important and the only way we are going to get a signal for that is to have a population study that has enough events, you know, to have confidence in the signal.

So I think that really is what you said a moment ago, and I think everybody around the table completely agrees with that. I do, and I am sure other do as well. So remember but in this situation as we haven't really dug into yet, you know, we have point estimates that are actually extremely favorable, and upper boundaries for the risk that are, you know, also very far away from the bars, at least one of the bars, that have been set. So, you know, we do have events. The question is, do we have enough events to be confident in them?

That's one question for us to deal with. If we feel like we have enough events to be confident that the signal is at least in a favorable direction the question becomes a different question. The question becomes a biologic question. You know, are you really going to see a different effect of the drug in a different population? I understand but I just want to sort of separate that's really a different question than just making sure you have enough events to see a signal. That's I guess my point.

DR. BURMAN: Thank you, let's see Mike you had a, oh I am sorry; you were indeed, thank you very much. Dr. Levitsky.

DR. LEVITSKY: So once again, coming at it from the youth end of things, I am hearing several things here. I am hearing an attempt to create stratification of who could use this medication. Yet we are dealing with the standard problem that you have in any trial, which is that these people because of the study but because of also the doctors who were working in this study were very well cared for.

They were on ACE inhibitors, they were on beta-blockers, they are on all sorts of stuff, which might not happen to someone else out there in the community, so they are already a special set. From the pediatric point of view, I understand it's hard to find anybody over the age of 17 who dies in an auto accident in this county, who doesn't have large vessel beginning disease. So what is coronary artery disease? Is it when you come in complaining that you are out of breath and your chest hurts? Or is it, I mean, how are you going to define this? Are you going to cath everybody before you are allowed in the study? I don't understand how you would define that. So my attitude toward this is similar to yours, which is that the biology suggests that there are not going to be adverse outcomes of this drug but I don't think we have the data right now to say that.

On the other hand, I don't think that it's reasonable, given what we know so far, to say that this drug needs a 20-year study before it can be released out on the market. I think it's just, it's a complicated decision governed by the meeting which discussed cardiovascular risks. I think that it also is a model for other drugs to follow, so we have to be very careful of what we do is fair to other drugs where the biology might be somewhat different.

DR. BURMAN: Can I ask you, what I think is the critical follow up question? Which is, are you satisfied enough that the pre-marketing data indicates there is a low risk and if that drug is approved that it should be approved for all patients with diabetes? Or would you take the view that there are insufficient data for the long-term and that it should only be approved for selected groups of patients with low cardiovascular risk, for example?

DR. LEVITSKY: I think that this drug, given what I know about it biologically, should probably be approved for all patients with very careful surveillance.

DR. BURMAN: I think that's a critical question, does anybody have a comment on that as well?

DR. TEERLINK: Just like to ask what she would surveil for?

DR. BURMAN: I didn't hear you John I am sorry.

DR. TEERLINK: I would like to ask what would you surveil for?

DR. LEVITSKY: Oh. I think that we would have to be looking for a risk of cardiac events and that's a very, just the long-term surveillance.

DR. TEERLINK: Oh, surveillance of the data, not of the individual patients?

DR. LEVITSKY: Oh no.

DR. BURMAN: Then let's see. Mike would you mind if Marvin goes first then get back to you, please?

DR. KONSTAM: Okay. I mean just to respond to your question, you know, I would say first I guess we should, I think we need to remind ourselves that the FDA has asked us about two bars, right? The first bar would be one of approvability. The other bar is, are we sure enough about the safety that no other studies are mandated?

So there are two bars here for us to grapple with. I think, you know, the question I am hearing you ask is if we think it reaches that first bar, would it be approvable for the entire population? What else would we need?

You know, I guess I would turn to the Agency about guidance but I think there are lots of options. I think, you know, you could restrict approval to the population at hand. That would be one thing you could do. An alternative approach would simply to say well, you know, you are approving it for the diabetic population with labelling that just simply states that there is not enough data to adequately assess the risk in a higher risk population. So the labelling could address this and then depending on what we say regarding additional studies, you know, if we are going to say additional studies are needed, we could drive that toward a high risk population.

DR. BURMAN: Thank you. Mike one more comment, we will move shortly to the question two.

DR. PROSCHAN: Yeah, actually Marvin addressed the first comment I had which was, you know, that really it's more than just that we are not seeing an increase in events in the treatment group but there is actually, you know, evidence going in the other direction. the other issue about the sub-groups, I mean this is just really hard to try and figure out, you know, even if your clinical trial enrolls people with heart disease, you know, you often don't have enough to really know whether the effect of the drug is different in that group than in the group without heart disease.

Dr. Henry pointed out that in the sub-group analysis there is just not enough data to be able to see whether there are different effects in different sub-group. So it's just, you know, even if you enrolled some people with heart disease at baseline,

even in that case will be very difficult to figure out whether the treatment effect is different in that group than in the group without cardiac disease.

DR. BURMAN: Thank you. Let me ask you, I know this is probably an impossible question to answer, but from a statistical standpoint what's the likelihood, given the data that we have, that we are missing a significant event of higher cardiac events at a larger population, even if it's the same population?

DR. PROSCHAN: So you are saying, what, how likely is it that what we are seeing is misleading?

DR. BURMAN: From a statistical standpoint, correct.

DR. PROSCHAN: Well, I mean that's what the confidence intervals address, basically. The upper limit of the confidence interval, you know, tells you how bad it could be and so I think, you know, these results do rule out significant harm at least, you know, if you look at the, the more specific the cardiovascular event, I think these confidence intervals do rule out, you know, much harm at all. If there is any harm it would have to be very small in this population.

DR. BURMAN: Thank you. Dr. Veltri.

DR. VELTRI: I just want to make a short comment and that is, with the CAS study, which was brought up before with the 1C antiarrhythmic agents, there is actually molecular basis for the harm that we have seen there and it's not Torsade, which is class 1A sodium blockage. It's 1C, where in an ischemic population where you provide potent sodium blockade and conduction block, when the ischemia occurs you shorten refractory periods, therefore you engage re-entrance cycle in the circuit.

So in CAS, I think in the ischemic population as opposed to non-ischemic population, there is a molecular basis for that. I think in this particular arena, I don't see

a pre-clinical signal for a molecular basis for this. Also, as has been said, in diabetes this is a continuum disease and a complex disease, so even the ATP 3 guidelines talk about patients at high risk and very high risk. So if you have coronary disease and diabetes, just like if you have ACS and smoke, that's a very high risk population as supposed to just a diabetic without CAD who is basically a CAD equivalent. So I think its complex, its complex.

DR. BURMAN: Thank you. Let me try to summarize this discussion, if possible, for point number one, before we move to point number two. So the issue with point number one is whether the low cardiovascular event rate in Saxagliptin clinical trials permit a reliable assessment of cardiovascular safety. This is a summary, albeit imperfect, that the studies only examine patients with low cardiovascular risk for a relatively short period of time, which may not be applicable to longer studies and higher risk patients.

Nonetheless, it appears that there is an acceptable cardiovascular safety risk done in post-hoc adjudication. There is question whether this low risk will apply to larger studies in patients who have a higher risk. It seems that many on the committee, maybe the majority, think that it may apply, or put in another way as Mike had said, the risk from a statistical standpoint of missing a significant cardiovascular event is low. Anyone have any, Mark, disagreement with that or modifications? All right, thank you.

Then let's move on to Question No. 2 and we will go for about a half an hour on this. This is a long question. Oh, you have it on a slide, thank you.

Question No. 2

Under the recent guidance regarding evaluation of cardiovascular risk for diabetes therapies ongoing and future diabetes drug development programs will be

required to conduct pre-planned adjudication of cardiovascular events and to collect all data necessary for such adjudication. However, the Saxagliptin development program was already complete by the time the guidance was issued. For Saxagliptin, neither pre-planned nor post-hoc adjudication occurred and full data were not available to permit meaningful assessment of many cardiovascular events.

The "SMQ MACE" and "Custom MACE" endpoints were defined post-hoc for a drug development program that was not designed to prospectively measure cardiovascular risk associated with Saxagliptin. Please discuss whether these endpoints and the post-hoc analyses permit a reliable assessment of cardiovascular safety. Please offer suggestions for improvements to the endpoints and analyses that may be applied to other diabetic programs that have already completed or had ongoing phase 3 programs at the time the Final Guidance was issued. Question No. 2 is now open for discussion. Sure, Marvin.

DR. KONSTAM: I mean I don't - I don't really have too much to say. I guess I wanted to use this opportunity to really thank the FDA because they really worked very, very hard on this and approached it, I think, in a sort of a difficult situation as systematically as I think you can, and were careful. They did a great job of describing their process that they used to get there. I guess, you know, to me again I think that's the best you can do in this kind post-hoc situation. You know, I think they described it well. I am sort of reassured that if I remember everything right the, you know, SMQ MACE data seem pretty similar to the companies, what you referred to as primary MACE. I think the fact that they came out sort of similar is reassuring to me.

DR. BURMAN: Correct me if I am wrong, I think it was the primary - the company's primary MACE.

DR. KONSTAM: I am sorry the custom. I didn't mean the SMQ MACE. The custom MACE was similar to the Prime MACE. I think you learn as you go. I think the discussion about creatinine kinase levels, you know, has emerged and, you know, I guess I share others concern that is extraordinarily nonspecific. I think going forward, you know, you might want to reconstruct it without that. You know, I think you're going to be left with the problem of, do you have enough events to count and that's a problem I guess that you can't solve by putting in a completely nonspecific element to it. So I mean I think you guys did a pretty good job.

DR. BURMAN: Thank you. Are there other comments? John?

DR. TEERLINK: So I would just want to second that the FDA has done, and the Sponsor, I mean everyone has done a great job analyzing the data we have. I think that one of the challenges I am having is; we actually have examples of multiple trials where there have been 40 events in a trial. That when the trial has been repeated with more events not only has a beneficial effect been shown, but it's been overwhelmed. So, all right, so I'll have to wait for that later.

DR. BURMAN: Are there any other comments?

DR. KONSTAM: I have one thing.

DR. BURMAN: Of course.

DR. KONSTAM: I think the other that's come up is the potential for inclusion of other kinds of events that indicate an ischemic event like, need for revascularization, you know, unstable angina like events that I guess might not be captured in the custom MACE one, that I think would be another direction that I would say might be very fruitful in looking for a meaningful broader event category.

DR. BURMAN: Thank you. Mike.

DR. PROSCHAN: Yes, there is just one more thing in terms of suggestions on how to analyze the data. There is one more way to handle data that has a small number of events and that is, instead of conditioning on the number of events, the total number of events across both groups, you don't do that. You say, is there any common event probabilities? Suppose the event probability is the same in the two groups. Is there any probability that would be consistent with the data shown? So there is just one more test, Statistic Bernard's test, which might be done in addition.

DR. BURMAN: Thank you. One statement is, please discuss whether these endpoints in the post-hoc analysis permit a reliable assessment of cardiovascular safety and given the limitations of the data, it seems like they might. Actually it's unknown because there is no real adjudication. All of us have participated in clinical trials where you may comment on an individual patient but adjudication, which is more strict, may or may not be accurate. So the real question is, how accurate is this post-hoc adjudication? Is it enough to then have these custom MACE and broad MACE to base the decision on at this point in time? Any comments? Dr. Veltri?

DR. VELTRI: It's the same comment I had before. I think the FDA has done a wonderful job in looking at this custom MACE concept. If you have a database where these CV death and mild stroke have been adjudicated, then you have that same database where you have investigative reports looking at specific MedDRA preferred terms, you can actually possibly compare the actual CEC adjudicated in these clinical trials versus the customized approach. I suspect that is going to be very close. I think that's one way of trying to validate this when you don't have the CEC adjudication.

DR. BURMAN: Thank you. Other comments?

DR. KONSTAM: Yeah, you know, I think you're very right. I think that the absence of adjudication and pre-specification are substantial limitations. There is no doubt about it, which is why I think the guidance document was written as it was. I guess the way I look at this is as a clinician that sometimes practices statistics at risk. You know, I guess the issue really is for us, what is the true confidence around the estimate? I guess in some way that we have no way to quantify. You know, when you don't have adjudication and you don't have pre-specification, these are things that make the confidence around a statistical test questionable, and make you need to widen the confidence around whatever, something that I'll call 'the true estimate' in some immeasurable way is.

What is reality? I guess sort of that, for what it's worth, that's the way I look at this, that, you know, you have a point estimate that happens to look really good in one direction, you have certain confidence around that. You really need to widen what you think the real confidence intervals are around that because you haven't really done it the way you like to do it. You don't have adjudication, you don't have pre-specification. Now that doesn't make it no data; these are real events that were really reported, that were of concern to the investigators, that were adjudicated as best we could post-hoc. It just makes the estimate of it much more difficult.

DR. BURMAN: Other comments on those issues? Because I would also like to re-emphasize the last part of this Question 2, which is, this isn't, I suspect, the only time we will be discussing this, or the FDA will be discussing this. What other suggestions do we have for improvements to present and future endpoints and analysis that may be applied to other diabetic programs that have already been completed or have ongoing phase 3 programs at the time the final guidance was issued. A difficult question,

but I like the committee's input on, besides looking at custom MACE and broad MACE, what else can we do? John, do you have some suggestions?

DR. TEERLINK: There are clearly fairly standard definitions for unstable angina, heart failure, myocardial infarction; these cardiovascular events have been used in this specific community. So certainly I would recommend that the current Sponsors look at those definitions and obtain as much of the information as possible to allow, even though it may be post-hoc adjudication. Also try to gear up to do as much adjudication as possible prior to breaking database lock and/or code break. If they still have to - if they are beyond that point then try to go ahead and, I think is what this Sponsor here tried to do, send it off to Duke. Obviously do it earlier. You folks knew this was going to be an issue. So give them more than four weeks to do it and as much possible information as is available, and try to do, you know, as close to the guidance document as possible.

DR. BURMAN: Mike.

DR. PROSCHAN: Go back to what I said before, I think that there is a huge problem here, which is that the drugs that have already been approved were not approved on the basis of long-term outcome trials. I think the idea of figuring out exactly what you want to compare it to, I mean, if you put someone on a background therapy that turns out to cause heart attacks, it may obscure any harm that the current drug, not your drug, causes. So I mean, ideally I think it would be best to just cancel all the approved drugs. I know this is not...Just cancel them all, make them do long-term placebo controlled trials. I know that's not possible but...

DR. BURMAN: That is just a modest proposal.

DR. PROSCHAN: Now the transcript doesn't record laughter and that's going to come out like you really meant it.

DR. BURMAN: Any other comments on this particular issue?

(No response.)

Then let me try to summarize this issue from part two and that is, all of us are uncomfortable with the post-hoc adjudication, which really is, the company is caught in between the regulation. So both the FDA and the company have done a fantastic job of trying to work out a system that helps determine whether there is an increased cardiovascular risk and all of us are uncomfortable with the data as it is. I think given the circumstances we agree that it's the best way it can be done and that there are some suggestions, as John had mentioned and Mike had mentioned, for future trials. There seem to me to be minor modifications because the data in most of these trials have already been collected.

Any additions or modifications to that brief summary?

(No response.)

Okay, then let's go to Question No. 3

Question No. 3:

The Saxagliptin trials included a 24-week, short-term, double-blind period followed by a long-term, double-blind period. Patients entered the long-term period if they completed the short-term period or if they were discontinued from the short-term period due to inadequate glycemic control. Patients who had entered the long-term period because of inadequate glycemic control during the short-term period were administered open-label rescue medications. Please discuss whether this trial design affects interpretation of cardiovascular results for the short-term period and for the combined short-term and long-term periods.

This question is open for a discussion. Well, I can start the discussion by saying I think the fact that they were rescued means that they didn't respond very well to the first therapy. So it does potentially alter the long-term therapy and I think we heard some statistical analyses that try to take those into account. The trials are imperfect but nonetheless in the real world seem reasonable. So does anybody have any further discussion on, important discussion on the long-term assessments and how they were done?

DR. KONSTAM: Well, you know, I guess I just don't have too much concern about, maybe I am missing something but I don't have too much concern about combining the long-term and short-term in this case. You know, from what I understand randomization was retained, blinding was retained, and it was a mixture between patients who simply continued the short-term and those who had glycemic rescue. I am not seeing a major problem with combining these populations. I don't know what others think.

DR. BURMAN: Dr. Flegal?

DR. FLEGAL: Well, I also, I don't see a major problem but there is the issue that Michael brought up of, what are the cardiovascular effects of the other medications? So it is kind of beginning to mix apples and oranges a little bit but some people are going through one treatment and some people are really not on the treatment they were originally randomized, so they have added another treatment that may also affect their cardiovascular risk. So I think it just muddies the waters a little bit.

DR. BURMAN: Mike.

DR. PROSCHAN: Yeah, I think from the standpoint of the HbA1c and the short-term trial, when I first looked in the booklet and I saw that it said, 'all the

analyses stop when you need to be rescued then you only count the value that occurred right before rescue'. My first reaction to that was, Oh, that's kind of icky because those are not randomized sub groups. on the other hand, it's consistent with what we do in blood pressure trials, which is, if you are trying to look at the change in blood pressure someone who hits a level that where they need to be treated with something else we do take the last, I mean we have in the past taken the last, observation right before they went on that additional medication. So it's consistent with what we have done when I was at NHLBI in those blood pressure trials. So I think it makes sense.

DR. BURMAN: If I may, for a point of clarification and I definitely could be wrong on this but, what you were just saying is implying that if someone in the short-term trial if they needed glycemic rescue they weren't included in the long-term trial.

DR. PROSCHAN: No, no, no. What I am saying is, for the purpose of seeing the HbA1c change they took, and I hope I am right about this, the value right before they had to go on the rescue medication. So that's just for the purposes of determining how much of an HbA1c change there was.

DR. BURMAN: Point of clarification is that correct?

DR. WOLF: Yes.

DR. BURMAN: Thank you. Are there any other comments?

DR. WYNE: I just had a brief comment about these events. I don't think I am concerned about lumping them all together partially because it's such small numbers. You would think that the people who go on to the rescue probably are at an increased risk of events. So on the one hand I was little bit curious about did the events all occur in the people who went on to rescue or was it evenly split between the people who stayed in their study and didn't need rescue.

Also one thing that was confusing to me is my recollection from the last couple of meetings of this committee, with respect to diabetes studies and events, is weren't we told that there tends to be an increase in events in the short-term, perhaps in the first six months, but then if you follow the people out for two to three years you get a decrease in the events in the treated group. So although it makes sense to me that there should be more events the longer you follow people actually what I think we are seeing here is even less events than we would have expected which maybe is a positive, that we are not seeing that increase in events in the first six months that we have seen with so many previous drugs.

DR. BURMAN: Thank you. I would like for clarification of that from any members of the FDA or the Sponsor respond to the second part of the question. I don't remember that myself...about there being less events in the longer term?

DR. PARKS: Dr. Wyne, are you referring to an advisor committee in July 2007? I think that's the only thing I can think of where there was some discussion about risk in short-term trials versus long-term trials. If that is indeed then the problem is that we are talking about not a single study or even a single data set here, they are two very different data sets, this is specific to the rosiglitazone advisory committee. The meta-analysis, which was comprised primarily of six months or shorter duration studies versus long-term studies that were three years, you really can't compare those two different data sets to say that the risk was different over time. Joy, do you want to comment on that?

DR. MELE: I was just thinking of proactive actually. Didn't we do some analysis where we were seeing some early events and then the curves came together?

DR. WYNE: I actually think it was a meeting prior to that but what I remember is a comment of, oh, yeah, this is typical in diabetes studies that we see an

early increase in events but that it goes away over time. Macrovascular events, yeah, not just microvascular events. It may just be it's because that statement was lumping together so many studies.

DR. BURMAN: Does the FDA have any further comments on that? Dr. Savage do you have a comment on that?

DR. SAVAGE: The thing that's commented on frequently was the DCCT and retinopathy, where there was an increase originally and then in the end there was a major benefit. I'm not really sure of an analogous situation in terms of cardiovascular disease and diabetes. You know, it may be that a study like ACORD if it's followed out long enough will show some type of a benefit because the total event rates were lower in the intensive group. I think the thing that frequently is referred to is the DCCT results.

DR. BURMAN: Thank you. Dr. Wyne maybe you could follow up as well. Did the Sponsor have a comment on that?

DR. WOLF: Given the limitations of our data set I think the thing that we have that provides some perspective on this would be the Kaplan-Meier curve; if we could project slide 57 from the core deck. So, again, we look carefully at the time course of when these events occurred and didn't, our view of the data is that we did not see evidence for increased harm for Saxagliptin either earlier or late. We looked at the same sort of data for all cause mortality and saw a very similar pattern.

DR. BURMAN: Thank you. We will take a break at 2:30. the first part of your question, if we can go back to that it, was whether those patients that have rescue and if my memory serves me right it's about 10-12% of people who were rescued are the ones that had a higher rate of cardiovascular events. Can anyone address that issue either from the FDA or the Sponsor? Please.

DR. WOLF: We specifically examined the issue of how many events occurred before and after rescue. We were prompted by the FDAs posing this particular discussion issue. If you could show slide 3-148 please. This slide describes the total number of events for primary MACE that occurred prior to rescue and number of events that occurred after rescue. As you can see on the slide, 10 of the 41 primary MACE events occurred after rescue. So most of them actually occurred prior to rescue. We have also done some sensitivity analyses where we have looked at the potential impact of rescue on these events. We used a Cox proportional hazards model where we included a time-dependant co-variate for rescue to try to tease out whether there was any impact of rescue. Please display slide 3-138.

At the top of the slide we display the un-adjusted Cox proportional hazard ratio for primary MACE. The second analysis is an analysis based upon including a time-dependent co-variate for rescue and a second co-variate for the baseline A1C. The final analysis includes only rescue as time-dependant co-variate, and our view of these data is that including a co-variate for rescue did not seem to impact the effect. Now, obviously there are limitations to these analyses, but based on these analyses we were not able to detect an impact of rescue. Thank you.

DR. BURMAN: Thank you. Any other comments on Question 3 before we break at 2:30 p.m. for 15 minutes and come back and discuss Question 4 and then go on to the voting questions?

(No response.)

Okay. Then what I would like to do is summarize Question 3. The issue here is whether the trial design, which was originally short-term period and then placebo-controlled in general or comparative control and then were administered open label

rescue medication. It seems that the consensus to the panel is that this, given the issues that we have discussed before, is an appropriate summary, and does give us significant information regarding the risks of cardiovascular and other events in this group. We further discussed and wondered whether there was a relationship between rescue and a higher rate of events and it didn't seem that that was so, and that also it seemed the longer a patient was studied the greater the chance of risk over time. Does that sound reasonable to the group? Then I would like to break, if the FDA has any announcements or anything. Then we will break from 2:30 p.m. to 2:45 p.m. and reconvene at 2:45 for the next question.

(Afternoon recess.)

DR. TRAN: Just a quick reminder; even though this is a public meeting, please do not cross the rope and approach the panel members during breaks or anytime during the meeting, thank you.

DR. BURMAN: Thank you Paul, I would like to move now to Question No. 4 and after discussion of Question No. 4, we will move on to the voting questions. With regard to Question No. 4, it states

Question No. 4

Multiple statistical methods were used to analyze cardiovascular outcomes. Please discuss the adequacy of these methods for measuring sensitivity of the results to analytical method.

This of course is a technical question that focuses on statistics. I would like to open it up for discussion and may be ask Mike as a statistician if he would be glad to answer part of the question.

DR. PROSCHAN: Right, yeah, no, I mean this is what I was commenting on earlier, I think in a case like this with not that many events, it's very important to look at a sensitivity analysis and to do it multiple ways. So I saw this as a definite plus. Like I said, the only thing I might do in addition would be this Barnard's Test, which can sometimes do - of course that's a test, it's not really for confidence intervals. I think the issues around like what analysis to do are kind of tricky, because if you condition on the total number of events, like I was saying, in some sense it was very natural, then you can't include trials with no events, because you just won't get any information out of those. in a way you see a trial with no events and you say, well, that's evidence that there may not be a problem, I mean or it's evidence we had such a low risk population that, you know, of course you didn't have a chance to see a problem.

So, I think it was good that they did some analyses that try to take into account the fact that you had no events, tried to use that information in some way and then some other analyses where you throw out the trial with no events. So, I thought it was very good seeing the analyses done many different ways and seeing similar results, what you don't see similar or not too similar results on are the custom MACE versus the more general MACE, I mean because the custom MACE has those - seems to show benefit where the more general MACE seems to show basically no effect. I don't exactly know what to make of that, I don't know how seriously to take those CPK elevations. In general, I thought it was very good to do the analyses many different ways and mostly getting similar results.

DR. BURMAN: Thank you. John.

DR. TEERLINK: So, I'm not a statistician. So I think when I try to hear about sensitivity analyses, I just have the clinical trial experience where we have a whole

series, actually the DCCT trial was an example that was almost stopped because of harm, because of low event rates, but then because they didn't believe it even though it was a statistically significant test with confidence intervals that were positive, were actually worse. So the point estimate was on the wrong side, the confidence intervals at 95%, confidence intervals were on the wrong side. They decided to keep going, because I said, you know, we don't really have enough events to evaluate what's going on here, and they decided to continue the trial and low and behold they found a big benefit.

We have a whole - after seventeen years. We have lots of examples from Vesnarinone, Losartan, Amlodipine, and a lot from my area in heart failure; that initial trials went one direction with small events. Then when the real trial was done with larger events, it went dramatically in the other direction. So I have this just sense of unease anytime you deal with just such small numbers, granted, you can do the same, you can do multiple statistical tests on the same numbers and that helps, but it doesn't get rid of the fact they are just really small numbers. So, one of the things that I propose, is later on, is to do kind of a simple sensitivity analysis saying, so how many more patients would have had to shown up in the Saxagliptin group to move the point estimate or the confidence interval into the 1.3, 1.8 test.

How many patients out of that 4000 plus trials would have had to have moved to have changed, and my guess is that number would be not big, I don't know how big, but probably not big, and that may give a better sense of - that's a true sensitivity analysis. Saying okay, if patients kind of moved one direction or the other, how confident are we and how sensitive are these numbers to the fact that we only have 40 events. I am not a statistician. I don't know the ways to do that, but that would have been helpful to me.

DR. PROSCHAN: I hate when these people start out with "I'm not a statistician" and then they make good statistical points. some of the examples that you are talking about involve monitoring over time and that's the kind of situation where if you look many times you are going to find sometimes it goes the wrong direction, and that's why we have to use monitoring boundaries to take that into consideration. Having said that though, you are correct that there have been some trials where they tried to repeat the trial, they thought the patients that they repeated the trial in were very similar, should have gotten the same results and they got different results. It does happen, and so, there is a limit to how confident that you can be, you know, how confident you could be, that's for sure.

I guess I am still reassured because sometimes in a situation like that with the small numbers, when you look at it using different statistical analyses you get different answers, then you feel even less secure, so. I think that it's well taken.

DR. BURMAN: Thank you. Dr. Konstam.

DR. KONSTAM: So, you know, I agree with Mike and John. Some of the examples that you use, number one, were in the course of monitoring with multiple looks being taken. Some of them were examples of subgroups; subgroup results that were not born out when the same question was asked in a unified prospective way. So those are all factors that you have to think about. I think we have to remember what is this question about, and sensitivity for what, for better or for worse, I think the bar that has been set for approvability with the understanding that we may request and mandate additional studies for greater degrees of confidence.

The bar that's been set is an upper confidence level of 1.8. So, I guess in thinking about that, I mean that's really the issue at hand, at least for the first part of our

next question, which is how do these different tests help us with regard to sensitivity for assuring us that we are below that bar. I guess, so what is the probability that we will go from the point estimate that we have with this one look that was taken but multiple methods that were used, what is the probability that that will go all the way to being above a 1.8 upper confidence limit. We are not asking that we be assured that this actually is a beneficial drug, right, its just - how sure are we that it's below the 1.8.

DR. BURMAN: Thank you John. Can I follow-up? You've mentioned several studies where there were - initial studies evaluation showed that there was a poorer outcome and then on the longer study, there was either neutral or better outcome. We discussed earlier, I just want to make sure you are not aware of any studies where there was no outcome or maybe even a beneficial outcome of the early studies, but over the longer term there was an adverse effect.

DR. TEERLINK: Actually, I was bringing up the list of studies. Those studies I listed had initially a favorable outcome and then demonstrated--

DR. BURMAN: I thought you got it the other way around.

DR. TEERLINK: So, yes. The Vesnarinone trial was an excellent example of one that was not post-hoc, it wasn't multiple visits, it was…

DR. KONSTAM: They were multiple groups, there were multiple groups in that.

DR. TEERLINK: It was a pre-specified look, and it was based on about at 40 events, so as were most of these. Most of these studies where they said, hey we've seen something here. It's the under the hundred event number, and they tend to cycle around 40 to 50. My point in the direct response to the question was for me, as a panel member, it would have been helpful to actually see some different, not statistical

sensitivity analyses per se, to say oh does it matter on, is the result sensitive to the different type of statistical test you implement, but rather how sensitive is it to possible random changes in patients from one group to the other, because it's so small, the number.

DR. BURMAN: John, excuse me. What was the trial you just quoted, I didn't understand you?

DR. TEERLINK: The Vesnarinone trials is one of them in terms of the groups.

DR. ALXEXANDER: Thank you.

DR. FLEGAL: I'm not a statistician either, but I may not be going to make any good statistical point, but we don't want to keep setting the bar higher and higher, we started out with 1.8 as encompassing the range and then we say, well, we want to have below 1.8 in all the subgroups or now we want to say, well, 1.8 if we had had more events, but I think we need to be careful about what we are - our goal is here is again not to show that this drug has a cardiovascular benefit, but to try to rule out major harm. So I think we need to be cautious about trying to impose too many conditions and really actually ending up making it more difficult than the guidance suggests to meet this criteria.

DR. BURMAN: Thank you. Other comments on this statistical question? Question No. 4?

(No response.)

All right. Then, let me, since we have time, let me open to just review the issue on question number four, and in my summary to see if this is accurate. Multiple statistical methods were used, please discuss the adequacy of these methods for

measuring the sensitivity, and I think we agree that they are reasonably sensitive, there could be a slight chance that they are wrong and over the longer term there will be a higher rate of adverse events, but that likelihood seems low. Okay. Everyone agree with that? Also I think we have time to, number one, go back and does anyone have any further comments on questions one through four that they want to bring up or for their discussion. Yes.

DR. WYNE: We just had a quick question we were trying to clarify earlier. All of these events in the custom MACE those were not first events, they were total events, correct?

DR. PARKS: No, all the analyses are of first events.

DR. WYNE: So there…

DR. PARKS: There weren't really multiple events in these studies.

DR. WYNE: Okay.

DR. PARKS: I don't know if the company wants to confirm them, but that's what I observed.

DR. WOLF: We agree with that, I believe - I recall there were two subjects who had more than one event, but it was really a minority of them.

DR. BURMAN: Thank you. Mike.

DR. PROSCHAN: I just want to make one more point about the 1.8 criterion. I think it would be helpful to sort of reframe that instead of - because it doesn't sound good, it doesn't sound good to say oh we ruled out a harm of a relative risk of 1.8. That still allows a possibility of a very harmful drug. So, I think it would be good to sort of rephrase that by, first of all, thinking in terms of one sided confidence interval instead of two sided, since you are really only concerned about one direction, and then may be

relaxing the percentage, instead of 95% confident, settle for 80% or something lower than 95, that way you can say, okay, we ruled out a harm of 1.3 or something rather than ruling out a harm of 1.8.

DR. BURMAN: Thank you.

DR. HENDERSON: As the consumer representative, I want to reemphasize the need for sub-group analysis. My only concern is the implication that it has cardiovascular safety for all people with diabetes. For example, if you've got grandpa and grandma over 65 years old, they are 10 years out from diagnosis of diabetes, they've been on Insulin, there is no data for that group of people, and like we said in our previous meeting, an absence of data does not mean safe. So, I would support earlier statements that the label includes insufficient safety data for these certain groups.

DR. BURMAN: Thank you. If there are no further comments, we certainly have time for discussion. I would want to - we'll move on to the questions in just a second. We have one further followup, Dr. Savage; you had a question that you wanted to ask that was of relevance.

DR. SAVAGE: Okay. I realize that dealing with issues of class effects of drugs is complex in its own right, but I wondered if there is any evidence that anyone knows of that the one drug in this class that has been approved and is out on the market is associated in anyway with any increase in cardiovascular risk, I don't know of it.

DR. PARKS: We would be in agreement with you on that.

DR. BURMAN: Thank you. Sponsors.

DR. WOLF: So, I feel a little uncomfortable talking about another Sponsor's drug. Merck has published data on the cardiovascular safety experience for Januvia, if I could please project slide 3-86. That's fair enough. I thought I was being

censored, I guess I was wrong. I would just like to call your attention to - so this is from a manuscript that was published just recently by Merck. The slide summarizes the cardiac disorder SAEs, Ischemia Related AEs, Ischemia Related SAEs and fatal Ischemia related outcomes. The Sponsor interpreted these data as not showing a signal; that was their assessment. If I could show slide 3-88, these are data for Vildagliptin, Vildagliptin is not approved in the United States. It is approved in Europe.

This slide represents odds ratios for Cardiovascular SAEs for Vildagliptin versus placebo and for all control groups. The point estimate is to the left of unity; the confidence intervals go past unity. Our interpretation of these data would be that we have not seen evidence for cardiovascular harm, for other members of the class, for where there are published data I just want to mention that the Vildagliptin data were also recently made available, and I think they were presented at the EASD in 2008, thank you.

DR. BURMAN: Thank you. Dr. Savage, any further follow-up? Then I just wanted to raise another quick issue, does anyone have any further discussion regarding other events? We focused on cardiovascular to a large extent, anybody have any questions for the Sponsor or the FDA regarding other safety signals besides cardiovascular?

(No response.)

DR. BURMAN: No. All right. Then let's move on to the Voting Question, if everyone agrees. We will be using the new electronic voting system for this meeting. Each voting member has three voting buttons on your microphone, yes, no and abstain. Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote. After everyone has completed their vote, the vote will be locked in, the vote will then be displayed on the screen, I will read

the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and their vote into the record as well as the reason why they voted as they did, however, before we vote we do want to have a discussion of the questions and let me - and we have the first question on the board, which is as follows, there are two questions to vote on.

VOTING QUESTIONS

Question No. 1

Based on the proceeding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that Saxagliptin rules out an unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?

A. If, voting "No," as we go around the room, we would like what additional cardiovascular data are needed to address any limitations resulting from the completed clinical development program and to support approvability including satisfying the 1.8 non-inferiority margin. In the past, when we've had questions, there has been active discussion regarding the questions, and I don't know if there will be or needs to be today, but I will open the discussion and ask for any comments regarding the question or clarification if someone doesn't understand it. This is a first, not only that, we may actually end early, no discussion? FDA, no? All right. Are we ready? Okay. Then as I just read in, the questions on the board, and we just vote, let me just give one last opportunity for discussion. Everybody is satisfied. Okay.

So question number one is on the board and is now eligible for voting.

DR. TRAN: Go ahead and press your vote. It will continue to blink. Don't worry about it. If you are unsure, re-press your choice again and we will capture everybody's vote. If you can all retry again please, your vote, and you are allowed to change your mind.

DR. BURMAN: The answer for the record is, the voting is "Yes" ten; "No," two; and "Abstain" zero. We will go around starting on this side, yes.

DR. LESAR: I voted yes.

DR. SAVAGE: I voted yes.

DR. KILLION: I voted yes.

DR. TEERLINK: I voted no. So, and that's mostly just to get into the record that I think - and may be this was an inappropriate way to use the vote, but I needed to actually say that I wanted to limit how it was labelled as well. I am not as comfortable saying yes for everything. This is okay. I don't think they proved that. It needs to be a relatively restricted patient population.

DR. BURMAN: Thank you.

DR. WYNE: I voted no. The reason is a combination of what Dr. Teerlink just said, and the fact that really the numbers of events are too low to provide an adequate assessment other than the fact it's a very restricted population. So it doesn't really give us a good overall assessment of cardiovascular safety.

DR. BURMAN: Thank you.

DR. LEVITSKY: I voted yes, but it was not a fully unqualified yes I had some of the same concerns.

DR. FELNER: I voted yes. I think according to the recommendations that were made this summer, that's the reason why this came up from the July conference

or the July meeting, and I think everything was done according to those recommendations. The signal is low for the question that's asked, the answer I think is yes. I don't see how you can come around it with the way the question is actually worded, if you want to add to the question, you can come up with a no answer, but the way the question is worded, it should suggest "Yes" based on what we had this summer with a very low signal, a low cardiac signal does not need further investigation.

DR. BURMAN: Thank you. Ken Burman I voted yes with a comment agreeing with the previous comments, and I think the Saxagliptin was caught in the interregnum between the former cardiovascular requirements and the new publication of guidelines in December 2008, and any effort to assess data in such a study will intrinsically have flaws and we've taken those into account to the best way we can.

DR. FLEGAL: I voted yes, and I also agree that within the limitations of the situation it's pretty consistent with what our committee discussed last summer that this evidences is sufficient given the limitations to meet those requirements.

DR. PROSCHAN: I voted yes also. I think that there is no question they ruled out 1.8, again I don't think that's the right way to phrase it, but overall, I think it certainly convinced me that there is not big harm.

DR. HENDERSON: I voted yes with a second to Dr. Teerlink's concerns about labelling.

DR. KONSTAM: I voted yes. Actually I first wanted to just bring out the comments that were made by two diabetic individuals today about the need for new diabetic, anti-diabetic therapies and I think this agent has promised to differentiate itself, specifically in getting glycemic control with potentially avoiding hypoglycemia, although I stress that the Sponsor didn't really show that, but there are some promise to that effect,

one has to consider that. I think the spirit of the guidance was that we ought to know something about cardiovascular risk for these drugs and the bar was set for approvability at ruling out an excess risk of 1.8 with a caveat that we can ask the Sponsor to do more post-approval and we are going to get to that in a moment. So I think that's a really important point, but I think the data as they are, with all the caveats that have been said, which I agree with, the lack of pre-specification, the lack of adjudication, I think are issues and certainly the numbers present limitations.

I am very reassured by how favorable the point estimate is, this might windup being a great drug, right? We don't know that yet. The point estimate is extremely favourable. The upper confidence limit is extremely far away from that magical 1.8 number. I am given more reassurance by the SMQ MACE endpoint, which admittedly is fairly non-specific, but at least gives me assurance again that we are very far away from that 1.8. I agree with the other comments that about the labelling I think the Sponsor did not study patients who are at extremely high risk including a large percentage of patients with known atherosclerotic disease and therefore I think there ought to be something in the labelling to the effect that those patients, that the safety in that kind of population has not been investigated.

DR. BURMAN: Thank you. I think that's everyone, good. Shall we move to the second question? The second question and the last question is;

Question No. 2

For the Custom MACE endpoint, the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratio was less than 1.3. These data involved a total of 11 cardiovascular events in the 24-week double blind short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study

periods of median 62-week exposure. Are these data adequate to conclude that post-marketing cardiovascular safety trials are unnecessary? (Vote required)

A. If voting "No" please comment on the limitations of the completed NDA program that will require an additional post-marketing trial(s). Discussion of that specific question or clarification?

DR. BURMAN: I think we are ready to vote. So please vote on Question No. 2, which is on the board in front of you.

(Voting)

Yes, we will read this unanimous vote into the record, "Yes" zero, "No" twelve, "Abstain" zero. We would like to go around the room maybe this time starting on the other side.

DR. KONSTAM: Well, what is there to say? I did vote no. I think, really picking up on the concerns that were raised by the people who voted no on the previous question. I certainly share those concerns when it comes to a higher level of confidence that there could not be harm here, which I don't think you can get there from here. I think the number of events is far too low from that, for that. I just would say and I do think additional trials should be directed to raising that confidence and the Sponsor ought to be extremely excited about doing those trials, because if they believe their point estimate, they are going to have a blockbuster drug, so we shouldn't get any resistance on that.

DR. HENDERSON: I voted no for exactly the same reasons that were just eloquently stated by Marvin.

DR. PROSCHAN: I voted no. Yeah, I worry about, first of all, I worry about not doing the long-term trial and then approving a drug and not requiring any

longer term trial regardless of the drug, I mean I just think it's a scary proposition here because of the fact that the adjudication of events, there is enough uncertainty there to make me feel even more like I do want to do a longer term trial and perhaps it would be nice to enroll people with coronary disease, so we can get evidence on that.

DR. FLEGAL: I also voted no for the reasons everybody stated, the point estimates are favorable, this is very encouraging, but there is a small number of events and lack of adjudication. So I don't think we really have enough data to be sure about this.

DR. BURMAN: I voted no. I agree with the previous comments and would echo the fact that a post-marketing study should include a longer trial with higher risk patients and assessing many of the issues we discussed previously not only cardiovascular risk and events in a codified manner. Also take high risk patients, assess other factors such as lymphocyte count, platelet count, look at pancreatic function and look at skin lesions potentially among some of the other issues that have been discussed. I voted no as well because our primary goal is to protect the patient population, I just don't think there is enough data in the studies that have been performed thus far to be absolutely certain that there is no risk or very little risk to many of the population studied.

DR. FELNER: I voted no and mainly driven by the comments from Dr. Teerlink and Dr. Wyne.

DR. LEVITSKY: I voted no and I agree with everyone, so I will say no more.

DR. WYNE: I voted no. I would like to, as people said earlier really complement the Sponsor and the agency and the work they've done in trying to evaluate this data and see if we could pull out any kind of cardiovascular safety data.

Unfortunately these studies were completed before the issue was raised and I just feel that the database available is inadequate to really address the cardiovascular safety issue. I think that data per se has very nice glucose lowering data, so I don't have any concerns about using it for glucose lowering, but I would like to know the long-term safety, and as has been specified from the cardiovascular point of view, it really needs to be ascertained in people at the highest risk, which probably includes more than seven to ten years of known diabetes.

DR. TEERLINK: I voted no as well, but I do want to share everybody's, I think, desire and happiness, that I think this is going to be, should be approved for and be available for patients and this as well as new therapies need to be made available in this area. Clearly, I think all of us believe that a new trial and a large high risk randomized trial needs to be done and otherwise, that's it.

DR. KILLION: I voted no, and is a conflicted or felt a little schizophrenic about this vote, having voted yes on the prior question, but the issue is a "Yes" or "No" vote doesn't admit to a lot of grey area. There are grey areas when we consider these things and so, I voted no on this question because I think that we are clearly - we had some ongoing concerns, but I want to credit the Sponsor for having said that they are interested and indicate that they are going farther with additional studies and that this is in the works and they will do a good job on that, I am sure. So, and that was why I voted no.

DR. SAVAGE: I voted no. I think several of the reasons have already been mentioned by people. I would like to just say a couple of things. It seems to me that the preliminary studies that are done on a drug prior to this type of thing clearly should include more data around the high-risk cardiovascular patients in the future. It

wouldn't be fair to apply that rule today, but on the other hand, it isn't fair to not insist on getting that type of data in the relatively near future, so that we can be sure that our optimism about the data that we've looked at is, applies across the whole spectrum of diabetic patients, I've been more struck in the last couple of years looking at the results of ACORD and the VA study and the long-term results of the UK PBS that the cardiovascular complications are more complex than many of us had thought and that we just need more data in that area.

I also think that the issue of avoiding hypoglycemia is important and something that there should be more data on, more because it could be that this drug is a safer drug to use under some circumstances. There wasn't enough data in terms of that or in terms of use in the elderly where there are some sluggish responses to hypoglycemia and so forth that might make them different from middle-aged patients, so I think that should also be monitored in a future study.

DR. LESAR: I voted no. For many of the reasons that have already been discussed and particular the need to study this drug further in patients with high risk.

DR. BURMAN: Thank you. I think this is an easy one to summarize in that everyone wants good post-marketing studies with the criteria that we mentioned earlier and I want to congratulate the committee for really doing a good job of walking the fine line between preserving patient safety and yet trying to move drugs in this transitional period into the market. I would like to ask if the FDA has any other comments or questions that they would like to bring up at the present time, No? Anybody have any other issues?

(No response.)

Hearing none, I would like to publicly thank several groups, number one, the FDA and everyone that I worked with there including Dr. Parks, Dr. Jaffy and Paul Tran have been wonderful, and thank you all for your accessibility and hard work. I would also like to thank the Sponsors for a very nice presentation and evaluation of the data and of course thank each of the committee members for their hard work and contemplation on these issues. Hearing no other issues or comments, I would like to adjourn the meeting at this early hour, thank you.

(The Endocrinologic and Metabolic Drugs Advisory Committee Meeting adjourned.)

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KEYWORD INDEX