Official Transcript

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Hilton Hotel
8727 Colesville Road
Silver Spring, MD 20910

April 2, 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 2, 2009

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Endocrinologic and Metabolic Drugs Advisory Committee
Hilton Hotel, Washington DC-SilverSpring
Silver Spring, Maryland
April 2, 2009-04-06

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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. Veltri, would you mind starting?

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

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

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. KILLION: I am Rebecca Killion; I am a Patient Representative and a type 1 diabetic.

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

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

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

DR. TUTTLE: I am Mike Tuttle, adult Endocrinologist at Cornell Memorial Sloan-Kettering Cancer Centre with a specialty in Thyroid Cancer.

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

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

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

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

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

DR. HENDERSON: Jessica Henderson, Consumer Representative.

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

DR. PAROLA: Tony Parola, FDA, Pharm/Tox Reviewer.

DR. DERR: Janice Derr, FDA, Statistics Reviewer.

DR. MAHONEY: Karen Mahoney, Clinical Reviewer, Division of Metabolism and Endocrinology Products, FDA.

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

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

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

DR. BURMAN: Thank you all very much. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and individuals can express their views without interruption. Thus s 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 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 meeting today. Also the committee is reminded to please refrain from discussing the meeting topic during break 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 exceptions of the industry representative, all members and temporary voting members are special Government

employees or regular Federal employees from other Agencies and are subject to Federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this Committee are in compliance with the Federal ethics and conflict of interest law. 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 and 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 discussions 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 or minor children and, for the purpose of 18 U.S.C. §208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves discussions Liraglutide injections Sponsored by Nova Nordisk, Inc. 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 all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for conflicts of interest.

With respect to FDA's industry representative, we would like to disclose that Dr. Enrico Veltri is serving as a non-voting industry representative, acting on behalf of all 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 the members and temporary voting members that if the discussion involves any other products or firm not already on the agenda for which an FDA participant had a personal or imputed financial interest, the participant needs to exclude himself from such involvement and their exclusion will be noted for the record.

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

DR. BURMAN: Thank you. Dr. Hylton Joffe will now have a presentation from the FDA.

INTRODUCTION AND BACKGROUND

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

Good morning, Dr. Burman, members of the Advisory Panel, ladies and gentlemen. My name is Hylton Joffe. I am the Lead Medical Officer for the Diabetes Drug Group at FDA. I want to welcome everybody back to Day 2 of our two-day

Advisory Committee meeting. Today we are going to be discussing a product from Novo Nordisk called Liraglutide, which has been developed as a new treatment for type 2 diabetes.

Just a few quick words before we get into the discussion at hand. I wanted to inform everyone of what the meeting objectives are for today. Specifically, we want to discuss whether there is adequate evidence of cardiovascular safety to support marketing of Liraglutide. There are thyroid related issues that we want to discuss today as well. One is the human relevance of thyroid C-cell tumors that occur at clinically relevant exposures in rats and mice and the other is the significance of several cases of papillary thyroid cancer in the phase 2/3 program.

With regard to cardiovascular safety, I want to remind the panel members that the same major issues we discussed yesterday for Saxagliptin apply today to Liraglutide. Again, just like with Saxagliptin, Liraglutide's development program was completed before the final diabetes cardiovascular guidance. Just like with Saxagliptin, the Liraglutide program was not prospectively designed to measure cardiovascular risk. Just like with Saxagliptin, there was no prospective or post-hoc adjudication and event rates are low. As I mentioned yesterday, we requested the same uniform analytical approach for both products. Again today, you will be hearing about "SMQ MACE," "Custom MACE" and that goal post of 1.8.

As I mentioned yesterday, although we used uniform analytical approaches, we do not want the panel members to make cross program comparisons. Liraglutide should stand on its own merits. The Liraglutide and Saxagliptin programs differ enough that cross program comparisons would not be appropriate.

A quick blurb on Liraglutide thyroid tumors; you will hear a lot more about this from the applicant. From the FDA, you will be hearing a non-clinical presentation by Dr. Anthony Parola. You will be hearing a joint clinical and statistical presentation from our Clinical Reviewer, Dr. Karen Mahoney and our Statistical Reviewer, Dr. Janice Deer. Basically, Liraglutide caused C-cell tumors in two animal species in both genders at clinically relevant exposures. Currently, there are no approved drugs that are known to cause C-cell tumors in two animal species. Some GLP-1 agonists that are under development may do so.

The applicant has conducted mechanistic studies to assist the clinical relevance of these animal findings and we will be hearing about that today. The applicant has also measured serum calcitonin in clinical trials and performed calcitonin stimulation testing in a subset of patients. FDA has reviewed all the above data, all cases of thyroid tumors reported in the Liraglutide clinical development program and you will be hearing more about these in a little while.

I just want to remind the panel members what the discussion points are for cardiovascular safety. The points you see on this slide are identical to the discussion points we had yesterday for Saxagliptin. On this slide, the second bullet point is specific only to Liraglutide. I mentioned this yesterday, but I will mention it again today. Several subgroup analyses of cardiovascular safety were performed for Liraglutide, comparing Liraglutide to placebo and to active comparator. I want to say up front that the primary comparison that FDA is interested in is Liraglutide to total comparator and the guidance does not discuss comparing 1.8 to subgroup analyses. Nonetheless, FDA is interested in hearing the panel discuss the relevance of the differences noted by type of comparator

and the role that these separate types of comparators could play in the evaluation of cardiovascular risk for future diabetes drug applications.

The cardiovascular safety-voting question that you will see today is identical to the one that we had yesterday for Saxagliptin. The second voting question we had for Saxagliptin yesterday does not apply today. There will not be a second cardiovascular safety voting question. With regard to the thyroid tumors, we would like the panel to discuss the following issues:

We would like the panel to discuss whether the applicant has provided adequate data to show that the treatment related thyroid C-cell tumors are rodent specific and not relevant to humans. I would like the panel to discuss the calcitonin findings from the clinical trial data and would like the panel to discuss the numerical imbalance of papillary thyroid cancer reports in the Liraglutide clinical trials.

After that, we will ask the panel to vote on the following question; Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans? If voting yes, why and if voting no, please explain why and provide recommendations for clinical trial monitoring for thyroid C-cell tumors in the development programs for other GLP-1 analogs.

As a second question, we will ask assuming the reminder of the risk benefit data are acceptable, do the available data on thyroid C-cell tumors permit marketing of Liraglutide? If voting yes, why. We would also want the panel members who vote yes to also comment on the need for an approach to post-approval risk management. For example, for Liraglutide treated patients, does there need to be a baseline assessment or ongoing monitoring for medullary thyroid cancer and if so, what

types of assessments should be done. If voting no, why not and what additional data related to medullary thyroid cancer are needed to support marketing.

The last question is identical to the question I just read except that it asks about papillary thyroid cancer instead of medullary thyroid cancer. With that, I will turn over the mike back to the Chairman. Thank you everyone for coming and we look forward to a thoughtful discussion on these topics.

DR. BURMAN: Thank you. We will now proceed with the Sponsor's first presentation. 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 and that the schedule indicates we will have the Sponsor presentations from 8:15 to 9:45 with 15 minutes then for questions to the Sponsor. Good morning.

SPONSOR PRESENTATION

NOVO NORDISK, INC.

INTRODUCTION

MARY ANN MCELLIGOTT, PH.D.

Good morning ladies and gentlemen of the FDA and members of the Advisory Committee. I am Mary Ann Mcelligott, Associate Vice-president for Regulatory Affairs at Novo Nordisk. We submitted our new drug application on May 23rd, 2008. We are pleased to be here today to present data demonstrating that Liraglutide is an important and needed treatment option in diabetes therapy.

Liraglutide is an analog of human GLP-1. In all studies in our program, Liraglutide significantly improved glycemia control, achieving the primary regulatory endpoint. Liraglutide also met several clinically relevant secondary endpoints consistent

with ADA guidelines. Notably, treatment with Liraglutide was associated with weight loss.

Liraglutide is generally well tolerated with GI side effects the most commonly reported. Overall, studies demonstrated that glycemia targets were achieved with a low risk of hypoglycemia. Our proposed indication is treatment as an adjunct therapy to diet and exercise to improve glycemia control in patients with type 2 diabetes for use as monotherapy and in combination with one or more current treatments. Dosing is once daily and independent of meals and time of day based on the long half-life. Patients are initiated on a dose of 0.6 milligrams for one week then increased to 1.2 milligrams. After at least a week and based on clinical response, the dose can be increased to 1.8 milligrams to achieve maximum efficacy.

For our presentations today, Dr. John Buse from the University of North Carolina and former president of the American Diabetes Association will discuss the rationale for additional therapies. Dr. Alan Moses, the Global Chief Medical Officer at Novo Nordisk, will present the unique pharmacology of Liraglutide. Dr. Milan Zdravkovic, the head of our GLP-1 clinical program, will review our extensive development program that demonstrates the efficacy and safety of Liraglutide. Dr. Gilbert Daniels, Co-Director of the Thyroid Clinic at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School, will provide the clinical perspectives on thyroid and calcitonin. Dr. Moses will conclude by summarizing our favorable benefit risk profile and our proposed risk management plan for Liraglutide.

Today we also have several experts to assist us in answering any questions you may have on our cardiovascular risk assessment as well as other areas of interest. We believe our data demonstrate Liraglutide's high glycemia efficacy and favorable

safety profile and we have a risk management program to responsibly manage post-marketing safety. We have specifically organized this presentation to address the questions FDA has posed to you as you consider the approvability for Liraglutide. I now introduce Dr. John Buse from the University of North Carolina.

RATIONALE FOR DEVELOPMENT OF

NEW DRUGS FOR TYPE 2 DIABETES

JOHN B. BUSE, M.D., PH.D.

Chairman Burman and members of the Advisory Committee, thank you for the opportunity to speak to you today. I've worked in the field of diabetes for over 25 years and have a broad perspective as a clinician and as an investigator in large-scale clinical trials. Let me set the stage for why we need additional drugs to improve treatment options for people with type 2 diabetes.

Diabetes has reached epidemic proportions in the US and has created a major challenge for our healthcare system. Over the course of a lifetime, one in three Americans will develop diabetes. Today, more than 7.5% of the US population, or 23 million people, have type 2 diabetes and more than 1.5 million new cases are diagnosed annually. Indeed, in the time it takes for this Advisory Committee meeting, over 1,500 people in the US will develop diabetes. Diabetes is a leading cause of death and disability. The personal and societal impact of diabetes requires more effective therapies because even with a large number of classes of diabetes drugs available today, too few patients achieve target levels of control.

To address the challenge of diabetes, the American Diabetes Association and the European Association for the Study of Diabetes established a consensus panel, of which I was a member, to develop and subsequently revise a treatment algorithm for type

2 diabetes. Our most recent report was published in January. We included treatments in the algorithm based on six criteria: 1) Glucose lowering effectiveness, recognizing that there is a large range among diabetes treatments. 2) Non-glycemia effects that may influence the risk of long-term complications. Specifically mentioned were effects on CVD risk factors, body mass, insulin resistance, and insulin secretory capacity. 3) Safety. 4) Tolerability. 5) Ease of use. 6) Expense.

One of the major changes in the 2009 algorithm was to include GLP-1 agonists as second tier therapy as an add-on to metformin because of their strong efficacy, particularly when hypoglycemia is a clinical concern or weight is of particular concern for a patient. We did not include DPP-4 inhibitors in the algorithm at this time.

Why was the category of GLP-1 receptor agonist added to the revised treatment algorithm? In part, this was because we recognize that each of the current therapies has some limitations. Metformin causes GI intolerance and should not be used in patients with renal insufficiency. Sulfonylureas are associated with hypoglycemia and weight gain and their efficacy tends to wane over time. Insulin is highly effective, but causes hypoglycemia and weight gain and its use are met by resistance by patients and physicians alike. Finally, the thiazolidinediones, including pioglitazone, are associated with weight gain, bone fractures and fluid retention increasing the risk of congestive heart failure.

The GLP-1 receptor agonist, of which Exenatide is the only currently available agent and of which Liraglutide is being considered for approval today, have the potential to improve diabetes treatment based on strong glycemia efficacy, positive extra glycemia effects and low risk of hypoglycemia. We can all agree that diabetes is a serious problem in the US. Despite broad advances in treatment, most patients do not

achieve adequate control of diabetes and its comorbidities. As the updated ADA/EASD treatment guidelines reflect, GLP-1 agonists offer great promise in the treatment of type 2 diabetes.

Within this class, there is room for new agents with the potential for greater efficacy, longer duration of action, and better tolerance. As a practicing clinician faced on a daily basis with patients struggling with the challenges of diabetes, I believe that GLP-1 agonists like Liraglutide will play an increasingly important role in treatment regimens. Thank you for your time. I will turn the podium over to Dr. Moses.

GLP-1 PHARMACOLOGY

ALAN C. MOSES, M.D.

Thank you, Dr. Buse. Good morning ladies and gentlemen. This morning, I will review the physiologic effects of GLP-1, provide some insights into why these effects are highly relevant for the treatment of type 2 diabetes and then introduce you to the structure and pharmacology of Liraglutide.

Glucagon-like peptide-1 (GLP-1) is a 31 amino acid peptide secreted by the GI tract. It's a member of the incretin class of peptide hormones. So named because they enhance insulin secretion when glucose is administered orally compared to when it is administered intravenously. The primary target of GLP-1 is the pancreatic islet where it promotes glucose dependent insulin secretion and glucose dependent glucagon suppression.

The half-life of native GLP-1 of 1.5 to two minutes is too short to conveniently provide the 24 hours tissue exposure to GLP-1 necessary for its full impact on glucose levels. As this slide illustrates, even after seven days of treatment, the 16-hour infusion of native GLP-1 shown here in blue is insufficient to control blood glucose

levels over 24 hours because when the infusion is stopped, blood glucose rises quickly. As a result, there is no effect on fasting plasma glucose the following morning. The curve in yellow demonstrates that a full 24-hour infusion of native GLP-1 lowers glucose throughout the day including the fasting plasma glucose the next morning.

As Dr. Joffe outlined yesterday, there are two approaches to enhancing GLP-1 action in diabetes. Inhibition of GLP-1 degradation by dipeptidyl peptidase-4 (DPP-4) as you heard yesterday and administration of exogenous GLP-1 receptor agonist. Inhibition of the incretin-degrading enzyme, DPP-4 increases GLP-1 plasma levels by two to 2.5 fold. DPP-4 is a ubiquitous enzyme with multiple targets that increases the levels of multiple bioactive peptides. GLP-1 receptor agonists interact with a highly specific cell surface receptor distributed on physiologically relevant target tissues. The biologic effects are determined by receptor distribution and tissue receptor density. GLP-1 receptor agonists produce pharmacologic levels of biologically active GLP-1. The pharmacokinetics of the agonists determine the duration of the response.

A goal of therapy then is to identify approaches for producing pharmacologic levels of GLP-1 receptor agonists for a full 24 hours. Novo Nordisk set out to modify native human GLP-1 to make its pharmacokinetics appropriate for 24-hour exposure. This slide illustrates the structure of Liraglutide. Liraglutide has been engineered to be 97% identical to native human GLP-1 by modifying one amino acid residue, that is substituting arginine for lysine at position 34, and by attaching a C-16 fatty acid with the glutamic acid spacer on the remaining lysine residue.

With its 97% homology to human GLP-1, Liraglutide differs substantially in structure from the other member of the GLP-1 receptor agonist class that is current on the market. This slide illustrates how the pharmacokinetics of Liraglutide render it

appropriate for once daily administration at any time of day and unrelated to meal ingestion. Peak plasma concentrations occur after 12 to 13 hours. The plasma half-life is approximately 13 hours in duration resulting in substantial Liraglutide blood levels for greater than 24 hours after a single dose. Peak plasma levels and AUC are both dosed proportionally. The mechanisms underlying this prolonged PK profile include Liraglutide self-association which delays absorption, resistance to degradation by DPP-4, and albumen binding.

This slide demonstrates the glucose dependent action of Liraglutide on insulin secretion. As shown in the gray line, individuals with diabetes have decreased insulin secretion in response to increasing glucose levels. When treated with Liraglutide and this was single dose the night before, illustrated by the orange line, insulin secretion improves nearly to the level of individuals without diabetes, which is shown in blue. Liraglutide does not stimulate insulin secretion at low glucose levels.

Thus Liraglutide does directly improve beta cell function in people with type 2 diabetes. Both the pharmacokinetic and pharmacodynamic characteristics of Liraglutide predict that Liraglutide should substantially improve glucose control in Type 2 diabetes with a low risk of hyperglycemia. With this as background information, I will now ask Dr. Milan Zdravkovic who is head of our GLP-1 development program to review the efficacy and safety of Liraglutide. Milan?

EFFICACY AND SAFETY PROFILE OF LIRAGLUTIDE

MILAN ZDRAVKOVIC, M.D., PH.D., MSC PHARM MED

Thank you, Dr. Moses and good morning ladies and gentlemen. Today, I will start by giving a background on the phase 3 program. I will then present data on the primary glucose lowering endpoint, hemoglobin A1c, followed by data on hypoglycemia

and the weight lowering effect seen with Liraglutide, two factors that are traditionally trade-offs in lowering glucose levels. I will then turn to a discussion on safety which will focus on two main safety areas as also presented in the FDA briefing document, being the rodent thyroid C-cell findings and the cardiovascular safety.

This was a global development program conducted in more than 40 countries. The submission consists of 40 clinical trials including five phase 3 trials. The NDA included more than 6800 people of which more than 4600 people were treated with Liraglutide hereof 2500 included in phase 3 trials. We designed the clinical program to start Liraglutide across the spectrum of type 2 diabetes. From the early segment of patients failing on diet and exercise in monotherapy study code 1573. To the segment of patients failing on one oral anti-diabetic drug, OAD, being the sulfonylurea combination study 1436, and the metformin combination study 1572. Through the segment of patients failing on two oral agents, being the metformin plus thiazolidinedione combination study 1574, and the metformin plus sulfonylurea combination study 1697.

All phase 3 studies were randomized, controlled and double blind. To get the best possible understanding of Liraglutide's effects, we compared it both to background therapy plus placebo as well as other widely used therapies. Therefore, the placebo group is used as a term for the randomized background therapy plus placebo and is not just simply placebo. This is also of importance when we later discuss comparative groups and cardiovascular safety. All studies, except the monotherapy study, included a placebo group. As regards to active comparators, then in the monotherapy study, the effect was compared to glimepiride, in the SU combination study to a thiazolidinedione and in the metformin combination study to glimepiride. In the metformin plus SU study

to the basal insulin glargine. The glargine arm was open label with a titration algorithm adapted from the Lantus trial.

The doses chosen for the active comparators were the highest doses approved across the countries participating in any given trial. We tested three data doses of Liraglutide from 0.6 to 1.8 milligram per day. All combination therapy studies had a primary duration of 26 weeks and the monotherapy study had a primary duration of 52 weeks.

On the next two slides, I will give a more detailed description of the study designs. In the monotherapy study, people with type 2 diabetes were eligible if their hemoglobin A1c was 7% or higher. Subjects were randomized based on fasting plasma glucose and if randomized, patients who underwent these would discontinue these and start on randomized therapy. The primary phase of 52 weeks was double blind and subject's hereafter entered into an open label control extension for four years giving a total duration of five years. All subjects in the extension are maintained in the randomized arms and the study is currently in its third year.

There is an example of one of the OAD combination studies that also included an extension phase. Screening HbA1c was to be higher than 7%, but the subjects could be treated with any OAD in mono or in combination therapy. People not on metformin would discontinue their OADs and start a forced run-in metformin period followed by a maintenance period. A similar run-in approach was used in the other combination studies. If FPG was within the prespecified range, subjects would be randomized. The primary phase of 26 weeks was double blind and subjects hereafter entered into an open-label control extension for 76 weeks giving a total study duration of

two years. Again, all subjects were maintained in the randomized arms. The extension phase has recently been completed.

I will review the phase 3 efficacy data trial by trial. The safety presentation will be based on a pooled analysis across studies. The primary duration of the phase 3 studies was 26 and 52 weeks. Data beyond 52 weeks would exclusively be from open-label, but controlled extension studies. Randomization was maintained in the open label studies and therefore this provides valuable data on the longer-term efficacy and safety profile of Liraglutide. This is of importance when we later discuss calcitonin and cardiovascular safety data.

Based on the 120-day safety update, we included data from 700 subjects exposed to Liraglutide for 76 weeks or more. The main inclusion criteria in our phase 3 program were subjects with type 2 diabetes and hemoglobin A1c in the range from 7 or 7.5 to 10 - 11%, depending on the trial, aged between 18 and 80 years, a BMI of less than 40 to 45 again depending on the trial. The most important exclusion criteria were treatment with insulin, impaired liver and kidney function, history of myocardial infraction within six months or heart failure Class I through IV or III through IV depending on the trial and the control therapy included. A more detailed description of these can be found in our briefing document.

The primary endpoint in the studies was hemoglobin A1c. This is a validated surrogate marker from microvascular complications. All the prespecified secondary efficacy endpoints included body weight, we also looked at fasting and postprandial glycemia control, blood pressure and lipids. The main safety endpoints included adverse events, hypoglycemia and safety lapse. For hemoglobin A1c, the trials were powered for a superiority difference of 0.5% points against placebo and for a non-

inferiority margin of 0.4% points against the active comparators. All five therapeutic confirmatory trials included a pre-defined hierarchic testing procedure allowing non-inferiority and subsequent superiority testing while protecting the overall type I error rate. Details are shown here and in the briefing document.

We studied a representative population of people who would be eligible for further glucose lowering therapy. There was a balanced representation of female and male subjects. As expected, the duration of diabetes increased from the monotherapy study through the combination therapy studies. The average hemoglobin A1c across studies was just more than 8%. Also BMI and weight were elevated in this population demonstrating the need for therapies that can lower weight. There was a high completion rate in the five studies. The highest rates were found in the Liraglutide and active comparator groups and the lowest in the placebo group. This difference was due mainly to ineffective therapy, which was most frequent in the placebo group. Adverse event withdrawals occurred in around 8% of people at the two higher doses of Liraglutide and were less than 4% in the controlled groups. This was related to a higher frequency of gastrointestinal side effects.

Now, turning to the efficacy results. If we start on effects on the glycemia control. Type 2 diabetes is a progressive disease and often hemoglobin A1c is seen to deteriorate in spite of treatment. In the monotherapy trial as shown here, there was a sustained effect on hemoglobin A1c following treatment with Liraglutide. At the end of the study, the change from baseline was 1.1% points for the 1.8-milligram dose and 0.5% points for glimepiride. Both doses of Liraglutide were significantly different from 8 milligrams of glimepiride. There was also a significantly greater lowering in A1c of the 1.8 milligram in comparison to the 1.2 milligram dose.

This slide illustrates the change in hemoglobin A1c from baseline showing that Liraglutide reduced A1c, the primary endpoint, significantly more than placebo across all studies. The 1.8 milligram dose lowered hemoglobin A1c by on average one to 1.5% points versus baseline. Significant differences in comparison to the active comparators were observed in three out of four studies; in monotherapy versus glimepiride, in SU combination versus Rosiglitazone, and in metformin plus sulfonylurea therapy versus insulin glargine.

Looking at the percentage of people reaching the American Diabetes Association A1c target of less than 7, we see that Liraglutide brings significantly more to target levels than placebo. At 1.8 milligram, 42 to 53% of patients reached target levels. If we look at differences versus the active comparators, then we saw a significant difference in favor of Liraglutide in the same studies as where we also saw significant differences in hemoglobin A1c in monotherapy versus glimepiride, in SU combination versus Rosiglitazone, and in metformin plus sulfonylurea therapy, versus insulin glargine. Furthermore, we found that the 1.8 milligram dose of Liraglutide brought significantly more patients to target than the 1.2 milligram dose, in monotherapy, metformin combination therapy, and in the SU combination therapy studies.

As would be expected based on the 24-hour action profile, Liraglutide lowered both fasting and postprandial glucose levels. On both parameters, Liraglutide was significantly different from placebo. Additionally as would also be expected based on the hemoglobin A1c data, we also saw a significant difference versus the active comparators in monotherapy versus glimepiride and in the SU add-on study versus SU plus Rosiglitazone. Improvement in glycemia control may be associated with hypoglycemia. So, although this is a safety parameter, I will review this to you.

Based on GLP-1's glucose dependent stimulation of insulin secretion, a lower risk of hypoglycemia would be expected with Liraglutide. Furthermore, it's well described that hypoglycemia occurs more frequently when a GLP-1 analog is combined with a sulfonylurea. Generally, a low rate of minor events was observed in subjects randomized to Liraglutide. Few cases of major hypoglycemia were observed in subjects randomized to Liraglutide and the majority of these were seen in the SU combination studies.

Improvements in glycemia control are often associated with weight gain. On the next slides, I will discuss our observations on weight. The weight lowering effect of Liraglutide was sustained over time. In monotherapy, the reduction in weight reached more than two kilograms in the 1.8 milligram dose group and this is in contrast to the one kilogram weight increase following treatment with glimepiride.

Let's now review the weight data for all studies. We saw a dose dependent reduction in body weight across all of the confirmatory studies. The weight reduction at the highest dose was 2.8 kilogram from baseline and in all placebo control studies, except the SU combination study, doses of 1.2 and 1.8 milligram significantly reduced weight versus placebo. The weight difference of the 1.8 milligram dose versus the active comparators was from 2.3 to 3.8 kilogram in favor of Liraglutide therapy. This difference was significant in all studies.

Here I am showing data that subjects on Liraglutide are more likely to achieve a weight loss of 5% or more. At 1.8 milligram, this was seen an 11% in the SU add-on study, to 33% in the metformin combination study. In three out of four studies, there was significant difference compared to placebo. There was a significant difference

to the active comparator in all studies. Therefore, unlike several other therapies, Liraglutide not only improves glycemia control, but also promotes weight loss.

In summary, we found that Liraglutide improved the primary endpoint, change from baseline of hemoglobin A1c, not only versus placebo, but also significantly more than glimepiride and versus Rosiglitazone in combination with sulfonylurea and versus insulin glargine in combination with metformin plus sulfonylurea. Here the difference was within the predefined non-inferiority margin of 0.4% points. These changes were associated with up to 53% of patients being taken to an A1c level of less than 7%. In spite of the improvements in glycemia control, there was a lower risk of hypos. Furthermore, treatment with Liraglutide was associated with weight reduction with up to 33% losing 5% or more.

Given the focus of this meeting as also outlined in the FDA briefing document, I will focus on two key safety areas, being the rodent thyroid C-cell findings and the cardiovascular safety profile. A detailed description of the safety and tolerance profile of Liraglutide is included in the Novo Nordisk briefing document and we will be happy to discuss any question you may have. I will start by reviewing the pre-clinical data and the C-cell findings.

Our pre-clinical program was a stand up program conducted in accordance with global regulatory requirements. The pre-clinical safety profile documents that Liraglutide was well tolerated in animals. The effects of the compound were consistent with its pharmacological profile. Liraglutide was not genotoxic, state of the art genotoxicity assays were negative both in vitro and in vivo. Lifetime bioassays were conducted in rats and mice. These studies included a histopathological evaluation of more than 40 tissues from all major organ systems.

There was no general increase in overall tumor incidence. Two specific tumor types warranted a more detailed evaluation. These were dorsal subcutaneous sarcomas in male mice and thyroid C-cell tumors in rats and mice. A higher incidence of dorsal subcutaneous sarcomas was observed at the highest dose of Liraglutide in male mice. Importantly, the GLP-1 receptor is not present in these relevant cell types.

The literature reports different factors, which are associated with subcutaneous sarcomas in rodents. These factors are frequent subcutaneous high concentration injections and microchip implants used for animal identification. Both of these factors were present in the study. To summarize, since this was a single species finding and in one sex only and since this was only seen at the highest dose corresponding to more than 30 fold human exposure, we conclude that the dorsal subcutaneous sarcomas were not of clinical relevance.

Let's now turn to the rodent C-cell findings. In the mouse two-year study, C-cell adenomas were observed at 1 mg/kg and above corresponding to 13 fold human exposure. C-cell carcinomas were seen in a few female mice in the highest dose groups. In rats, the incidence of C-cell adenomas was increased at all dose levels with no safety margins for human exposure. A significant increase in C-cell carcinomas was seen at the highest dose in male rats. There was a substantial background occurrence of C-cell proliferation in rats, which is in agreement with the literature. Thus, both focal C-cell hyperplasia, C-cell adenomas and C-cell carcinomas occurs spontaneously in the rat. Liraglutide increase the incidence of these, dose dependently.

Before disclosing the rodent C-cell findings further, I will give some general information about the thyroid gland. The thyroid gland consists of follicular cells and C-cells or parafollicular cells which are found within the body of the gland. These

two cell types are distinct with respect to both origin and function. The follicular cells are of endodermal origin while the C-cells are of ectodermal origin. Papillary thyroid cancer is derived from follicular cells whereas medullary thyroid carcinoma is C-cell derived. Thyroid follicular cells secrete thyroid hormone and the C-cells synthesize and secrete the peptide hormone, calcitonin. Furthermore in rats, calcitonin is known to be more important for calcium homeostasis whereas in humans, the significance of calcitonin has been questioned. So, C-cell physiology is very different in rodents in comparison to non-human primates and men.

To understand the mechanism behind and the human relevance of the rodent C-cell findings, we performed more than 30 individual pre-clinical in vitro and in vivo studies. The in vitro experiments focused on describing the presence and function of the GLP-1 receptor on C-cells and assessing alternative mechanisms for the rodent findings. The in vivo studies focused on describing the relationship between calcitonin secretion and development of C-cell lesions. This also included assessing potential differences between rodents and non-human primates. These experiments included sensitive assessments of C-cell proliferation. Based on the literature, we hypothesize that the mechanism behind the rodent C-cell findings involved the following steps.

That the GLP-1 receptor known to be present on rodent C-cells is activated by GLP-1 agonists, that this causes release of calcitonin and in rodents, continued stimulation of the C-cell is followed by proliferative response which may lead to C-cell tumors. This general mechanism is parallel to what is known for other endocrine tumors in rodents. Importantly, we are not hypothesizing as suggested in the FDA briefing document that calcitonin in itself is the cause of C-cell proliferation. Rather, we have consistently found that calcitonin is a biomarker of GLP-1 receptor

mediated C-cell activation. It is well documented from a number of independent labs that rodent C-cells express the GLP-1 receptor. We confirmed this with immunohistochemistry from the rat thyroid.

In the left panel, a green calcitonin positive cell, a C-cell can be seen. In the right panel, the same cell is staying brown based on the presence of the GLP-1 receptor. The GLP-1 receptor was only found on C-cells and no GLP-1 receptor was seen on follicular cells. The FDA briefing document questions if the GLP-1 receptor is present on C-cells. As shown on the previous slide, our immunohistochemistry data showed GLP-1 receptor expression on C-cells. The validity of the immunohistochemistry data was confirmed by adequate controls documenting the specificity of the antibody. We also confirmed the GLP-1 receptor presence on C-cells and rodents by the use of in situ hybridization and in situ ligand binding. Our observations were consistent with the literature.

Functionality of the C-cells GLP-1 receptor was investigated in vitro. Here I show you results from a rat C-cell line. Again, we were able to confirm findings from other labs that the rat C-cell GLP-1 receptor is functional. On the graph, you see a dose dependent cyclic-AMP release in rat C-cells with three different GLP-1 receptor agonists being GLP-1, Liraglutide and Exenatide. The increased cyclic-AMP was followed by a dose dependent release of Calcitonin. Again, seen with the same three GLP-1 receptor agonist. Importantly, the effects could be antagonized with a specific GLP-1 receptor antagonist.

We compared the rat data to human data in vitro in the same experiments using the only available validated human C-cell line. Here we did not find evidence for a functional GLP-1 receptor. That is, we saw no increase in cyclic-AMP with Liraglutide

or other GLP-1 receptor agonists. Importantly, the cell line responded as expected to the positive control for scoring, shown in pink. Again, as would be expected based on the negative cyclic-AMP response, the three different GLP-1 receptor agonists caused no release of calcitonin. Having established the presence of a functional GLP-1 receptor in rodents, but not in the human cell line, we went on to perform a series of in vivo experiments in mice, rats and non-human primates looking at calcitonin and C-cells.

Here is the 24-hour profile for plasma calcitonin in mice after a single dose of Liraglutide. We found a dose dependent and sustained increase with Liraglutide at a magnitude of twofold or higher. Turning to the rat, I am here showing plasma calcitonin after a single dose of Liraglutide. Again, we found an acute increase in plasma calcitonin. We acknowledge that the effect was less pronounced in comparison to mice. This difference is due to a calcium loss in the urine, which lowers serum calcium and inhibits the release of calcitonin. After four weeks, there is no longer a calciuric effect and as can be seen on the graph, we see a dose dependent increase in calcitonin.

In summary, we found calcitonin to be a biomarker in rats and mice. We saw an early calcitonin release in both rodent species, which preceded C-cell proliferation. In mice, the calcitonin response was more pronounced. In rats, the calciuric effect of Liraglutide blunted the early calcitonin response. Chronically, the rat has a spontaneous development of C-cell proliferation followed by a marked increase in calcitonin. This masked the long-term calcitonin response in rats. However, the early calcitonin increase correlated with the later development of hyperplasia.

Given the findings in rats and mice, we turned our attention to the non-human primates, which are known to resemble humans in relation to C-cell physiology. In contrast to both rats and mice, no increase in calcitonin was found after a single dose

of Liraglutide in non-human primates. Similarly, no increase in calcitonin was observed in studies up to 87 weeks of duration. This was at doses corresponding to more than 60 x the human exposure. Importantly, the absence of C-cell activation translated into an absence of C-cell proliferation. In cynomolgus monkeys treated with doses for 12 months, we evaluated C-cell proliferation using the proliferating cell nuclear antigen marker (PCNA). The graphs on this slide show that there was no effect of Liraglutide on C-cell proliferation after 12 months of treatment.

In a different non-human primate study, we evaluated C-cell hyperplasia after 87 weeks of treatment. Again, we did not observe hyperplasia and again, this was shown at doses up to 60 x the human exposure. Evaluating the non-human primate model, it's not possible to do a classical lifetime assessment of carcinogenicity. However, it is possible to assess C-cell proliferation. The literature documents that C-cell proliferation in monkeys can be observed after only one month of dosing with Vitamin D in combination with calcium, which raises calcium and stimulates calcitonin secretion. Importantly, this validates our study methodology and provides reassurance about the lack of an effect seen with Liraglutide in monkeys of much longer treatment duration.

In the Liraglutide studies, we dose for up to 87 weeks and we increased the sensitivity for detecting C-cell proliferation. The data consistently documented the absence of any C-cell effects in cynomolgus monkeys.

When looking across species and combining the in vivo data, we found GLP-1 receptor mediated calcitonin secretion in both rats and mice. This preceded proliferation of C-cells. In contrast, we found neither calcitonin secretion nor C-cell proliferative changes in non-human primates. We looked into whether a non-GLP-1 receptor

mediated mechanism could be operational. Liraglutide was found to be highly specific for the GLP-1 receptor. In a broad screening panel with more than 75 receptors, Liraglutide was only found to bind to the GLP-1 receptor. This included receptors known to be present on C-cells and also receptors known to be involved in general cellular activation and growth. Additionally, confirming the GLP-1 receptor mediated nature of the findings, C-cell hyperplasia and neoplasia were induced with another GLP-1 receptor agonist in rodents.

So, taken together, we have demonstrated that the rodent C-cell effects remediated via the GLP-1 receptor known to be present on D-cells in rodents. If the GLP-1 receptor is activated, then calcitonin is released. Thus calcitonin is a biomarker for the process leading to C-cell proliferation. When comparing these effects on rodents to non-human primates, no similar effects were seen. That is, no evidence of C-cell activation, no calcitonin release and no C-cell proliferation in the non-human primates. However, to fully understand the human relevance, we also need to look at the human data.

We measured unstimulated calcitonin levels in more than 5000 subjects. Importantly, when evaluating the longer-term extension data, randomization was maintained allowing for a valuable assessment of the longer-term calcitonin profile of Liraglutide in humans. The 120-day safety update included data up to 18 months. Two-year data have recently become available and I will present these data in support of our findings from up to 18 months of exposure. We look for a biological activation of C-cells in humans by investigating changes in calcitonin in a multitude of ways.

This included looking at calcitonin over time both for mean values and outlier analysis. We also look for a change in calcitonin in people that had an elevated

calcitonin when entering our studies. To further increase the sensitivity of detecting changes in calcitonin levels and hence C-cell mass, we also performed a calcium stimulation test. This test was powered to detect a 50% difference in stimulated levels. I will start by reviewing the unstimulated calcitonin data.

This slide illustrates a geometric means of plasma calcitonin over the 104-week period from the two extension studies, monotherapy and Metformin combination therapy. As a reference, the upper normal range for calcitonin is 5 pg/ml on female and 8.4 in male subjects. The calcitonin assay was validated to a lower limit of quantification of 0.7 pg/ml. The geometric mean values were around one pg/ml in the entire two-year period. There is limited information on normal regulation of calcitonin in humans. A number of factors have however been suggested, including changes in glycemia control. There was an apparent variation in calcitonin levels for all groups.

We did not observe any meaningful changes in calcitonin compatible with C-cell activation. The FDA briefing document focuses on calcitonin levels at Week 12 and 26 since this is within the main part of some of the phase 3 studies. However, as calcitonin is a lab parameter and as randomization was maintained, we believe that it is valid and informative to look at the totality of the data. Looking at the same two-year data, now with 95% confidence intervals, then we see no increases over time in subjects on Liraglutide nor any apparent dose response relationships.

Looking only on mean values could mask relevant changes in the individual subjects. We therefore also looked at shifts in calcitonin. This table shows data on people who moved from below the upper normal range to above the upper normal range. The table shows data in six-month intervals up to 18 months. When looking at the distribution of subjects in each of the groups, then we found a comparable fraction of

subjects moving above this limit in all three groups. As mentioned in a Novo Nordisk briefing document, few subjects moved to a level of two times upper normal range or higher and a numerical imbalance could not be excluded. To investigate this further, we looked at individual calcitonin profiles over time in these subjects.

Here I show you data from male subjects. We found no apparent changes in calcitonin levels over time. Similarly when looking at individual female subjects, there were no increases in calcitonin over time. That is, the individual data did not indicate that their calcitonin levels were influenced by treatment with Liraglutide. It could be speculated that people with an elevated unstimulated baseline calcitonin level would be particularly sensitive to a C-cell stimulating effect and respond with an increase in calcitonin. We therefore also looked into the group of subjects with a baseline calcitonin level above two times upper normal range.

Again, when plotting the individual calcitonin levels over time, in this population, then we did not see any apparent increases in calcitonin in any group. In support of the GLP-1 receptor mediated nature of the rodent C-cell findings, then in rat C-cell adenomas have been observed with both Liraglutide and the marketed GLP-1 analog Exenatide. In the regulatory study, C-cell changes were not observed in mice with Exenatide, as this requires continuous 24-hour exposure. Therefore, it was of importance to understand whether there would be differences in the calcitonin response in humans between Liraglutide and Exenatide.

We investigated this in a clinical study including more than 400 people treated for a period of 26 weeks. The highest dose of 1.8 milligram of Liraglutide was compared to the highest therapeutic dose of 10 microgram of Exenatide given twice daily. As shown here, there were no differences in calcitonin levels between the two

therapies. We currently have an ongoing program with Liraglutide and obesity. As part of a 20-week dose range finding study with a 32-week controlled extension in more than 500 non-diabetic obese subjects, we also measured calcitonin. Beyond an opportunity to assess the effect of higher doses of Liraglutide also on a milligram per kilogram basis, then in the diabetes program, this segment of subjects is also an opportunity to look at calcitonin responses without confounding changes in glucose. This slide shows calcitonin data over up to 52 weeks. Again, there were no differences in calcitonin between Liraglutide and the controlled therapies.

We performed a calcium stimulation test in a subset of around 100 patients in two of the confirmatory studies to assess if changes in the maximum secretory capacity could be observed. We found no differences in the peak to basal ratio of stimulated calcitonin as shown here or in the peak calcitonin level. Finally, we also looked at C-cell pathology reports. As part of the development program, we intensively monitored the thyroid with calcitonin and also thyroid ultrasound in some trials. This screening program led to follow-up investigations during which six cases of C-cell histopathology changes were reported; two in the control group and four in patients randomized to Liraglutide. This distribution of cases was consistent with the approximate 2:1 randomization in the trials.

As also illustrated here, the majority of patients had existing thyroid abnormalities at baseline. If you look at the three cases of C-cell neoplasia in more detail, then in the control group, one case of medullary thyroid carcinoma was diagnosed in a subject with elevated calcitonin at baseline. In the second case, neoplastic C-cell hyperplasia or medullary carcinoma in situ in a subject with elevated calcitonin after

randomization. In Liraglutide, there was one case of neoplastic C-cell hyperplasia in a subject with elevated with calcitonin at baseline.

In conclusion, we believe that we have established the mechanism behind the rodent C-cell findings and that the findings are not of human relevance. When rodents are dosed with Liraglutide and other GLP-1 receptor agonist, the C-cell GLP-1 receptor is activated and calcitonin is released as an early biomarker preceding proliferation. In contrast, we have not seen activation of C-cells by Liraglutide in primates and humans, no increase in calcitonin when assessing this in a multitude of different ways and no C-cell proliferation in non-human primate studies. Based on this, we conclude that the C-cell findings are rodent specific and that the findings are not of human relevance. We also looked carefully at adverse events related to the thyroid gland in general. Here we did identify a numerical imbalance in papillary carcinomas and goiter that I will now describe in more detail.

This slide gives an overview of the diagnosed cases of papillary carcinomas in the development program. Five patients randomized to Liraglutide and one in the control group were diagnosed with papillary thyroid carcinoma. Four out of five subjects on Liraglutide as well as the controlled subject also had thyroid abnormalities at baseline. These baseline abnormalities that eventually led to thyroidectomy included an abnormal ultrasound or calcitonin at baseline prior to drug exposure. All cases except one were incidental papillary microcarcinomas of less than one centimeter.

One subject on Liraglutide did not have a preexisting thyroid disease and the incidental diagnosis was made due to an elevated calcitonin stimulation test. This subject was found to have a papillary microcarcinoma of one millimeter in size. In

summary, since papillary carcinomas are known to occur in around 10 to 30% of the population based on autopsy studies, we see the imbalance in the diagnosis of papillary thyroid carcinoma as a result of the imbalance in baseline abnormalities. This ultimately led to acquisition bias, that is an imbalance in the number of thyroidectomies being performed, led to a difference in the number of incidental diagnosis.

Similarly, when looking at the cases of goiter, while there was a numerical imbalance and the majority of cases were diagnosed in subjects that already had a preexisting thyroid disease. Let me now turn the microphone over to one of our external experts, Dr. Gilbert Daniels, Professor of Medicine, Harvard Medical School and Co-Director of the Thyroid Clinic at the Massachusetts General Hospital to put the C-cell and thyroid findings into a broader clinical perspective.

CLINICAL PERSPECTIVES ON THYROID AND CALCITONIN

GILBERT DANIELS, M.D.

Good morning. I've spent my career treating patients with thyroid follicular disease and C-cell disease. I've thought a great deal about the approaches to screening for and treatment of these conditions. I would like to provide a clinical perspective on three issues. Is there evidence that Liraglutide stimulates human C-cells? Two, is there any significance of the cases of thyroid papillary carcinoma identified in the Liraglutide development program? Three, what are the implications of screening for thyroid follicular and/or C-cell disorders?

Let's begin with a look at C-cell pathology in man. In careful microscopic studies on unselected thyroid glands, 33% are found to have C-cell hyperplasia. In the absence of hereditary medullary thyroid carcinoma, there is no evidence that C-cell hyperplasia is a precursor of medullary thyroid carcinoma or has any clinical

significance. Hence, there is no benefit in finding C-cell hyperplasia in the general population. If you screen 22,000 individuals, mostly with thyroid nodules, you will find that a half percent have medullary thyroid carcinoma.

Despite this, the American Thyroid Association does not recommend routine screening with serum calcitonin for medullary thyroid cancer even in patients with thyroid nodules. Based on my interpretation, a calcitonin screening program would lead to a great deal of unnecessary surgery. Why is this? Calcitonin levels are not accurate predictors of clinically significant C-cell disease until substantial elevations of calcitonin are present. Moreover, calcitonin measurements may be difficult to interpret based on a number of confounding factors. For example, proton pump inhibitors and H2 blockers, drugs readily available over the counter have been shown to double serum calcitonin concentrations and often produce calcitonin elevations.

It may be instructive to review a published study by Konstante of 5800 individuals with thyroid nodules who were screened with calcitonin measurements. 4.8% of these individuals had elevated calcitonin levels greater then 10 pg/ml. Only one in 200 patients with calcitonins between 10 and 20 had C-cell hyperplasia. For higher calcitonins between 20 and 50, only 8% had medullary thyroid carcinoma. In fact, only calcitonin measurements greater than 100 reliably predict medullary thyroid carcinoma. To put this in perspective, only one person had a calcitonin level greater than 100 in the Liraglutide program. This person was in the comparator group and the calcitonin elevation was present at baseline.

What's the difference in the effects of GLP-1 agonists on C-cells in rats and man? Spontaneous C-cell neoplasia is common in rats, but very uncommon in man. It’s well accepted that calcitonin is the marker of C-cell activation. The Sponsor’s data

convincingly demonstrate that GLP-1 agonist stimulate rodent C-cells, but do not stimulate C-cells in non-human primates. Importantly, GLP-1 agonists do not activate C-cells in humans as evidenced by a lack of stimulation of calcitonin secretion. Specifically, there is no increase in mean calcitonin levels over time up to two years. There is no increase in calcitonin levels even in people with elevated baseline calcitonin.

Let's look at the C-cell pathology in the Liraglutide development program. There were six cases of C-cell pathology; four in the Liraglutide group and two in the comparator group consistent with the 2:1 randomization. Four cases of C-cell hyperplasia, one with nodule or neoplastic C-cell hyperplasia were identified in Liraglutide group. Three of these four patients already had elevated calcitonin prior to study drug administration. One medullary thyroid carcinoma and one medullary thyroid carcinoma in situ were identified in the non-Liraglutide treated subjects. The four subjects on Liraglutide with histologically proven C-cell hyperplasia had no consistent change in unstimulated calcitonin levels in response to Liraglutide administration. Thus, there is no evidence that the six cases of C-cell pathology were related to Liraglutide administration.

Now, let's turn our attention to thyroid follicular cells. The thyroid follicular cell is distinct from the C-cell in origin, abundance and function. Thyroid follicular cells can give rise to goiters, nodules and papillary thyroid carcinomas. There is no evidence for disorders of the follicular cells in response to GLP-1 agonists like Liraglutide in any animal models, including man. For context, thyroid nodules are very common in the population in both men and women. 5 to 10% of individuals have thyroid nodules by palpation. Moreover, conducting screening ultrasounds will increase the identifications of nodules by five to 10fold.

As a result, ultrasound screening would dramatically increase the number of people requiring unnecessary thyroid surgery. If I were to screen everyone in this room with a thyroid ultrasound, 20 to 50% of you would have thyroid nodules over one centimeter in size. About 25% of you with thyroid nodules will require thyroid surgery with potential complications. Less than half of those having surgery will actually have overt papillary thyroid cancer, about 10% of those with nodules. Most of you with thyroid nodules not having surgery will be unnecessarily frightened.

In addition, 10 to 30% of the general population has microscopic papillary thyroid carcinoma, that is those less than one centimeter in size. This is almost always an incidental finding of no clinical significance. 98% of individuals with papillary thyroid microcarcinomas are never discovered in their lifetime. A thyroidectomy for any abnormality based on screening will also increase the detection of unsuspected and clinically insignificant thyroid abnormalities such as papillary thyroid microcarcinomas. This is the clinical equivalent of examining thyroid tissue at autopsy.

Why despite this high prevalence of thyroid cancer, does no major thyroid organization recommend screening for thyroid nodules in papillary thyroid cancer? Although the incidence of thyroid cancer has increased significantly, growing 250% in the last 35 years, this increase has been driven by finding small papillary thyroid carcinomas under two centimeters. Most importantly, the mortality from this disorder has not changed over the same period of time due to the low mortality from small papillary carcinomas.

The FDA has raised the question of whether Liraglutide causes papillary thyroid carcinoma. Let me tell you why the data do not support an association. Five cases of papillary thyroid carcinomas less than 1.5cm were identified in individuals

treated with Liraglutide. All cases were identified incidentally by thyroid screening procedures. Four of the five cases on Liraglutide at elevated calcitonin levels; three at baseline and one case was identified by screening ultrasound. Based on these findings, it was the screening program that led to the diagnosis of clinically insignificant papillary thyroid carcinoma. Thus, there is no evidence that Liraglutide caused these small papillary carcinomas.

Based on my interpretation of the data and my extensive clinical experience, I believe that there is no relevance of rodent C-cell findings for humans, that papillary thyroid carcinomas identified in this development program were incidental diagnoses based on screening procedures and importantly, that screening for thyroid follicular in C-cell disease is not warranted nor recommended based on all available data. Thank you.

DR. ZDRAVKOVIE: Thank you, Dr. Daniels. The second focus area in my safety review is cardiovascular safety. Let's initially look at the cardiovascular biomarkers, blood pressure and lipids. Based on encouraging data from phase 2, blood pressure was a prespecified endpoint in our phase 3 studies. We found reductions in systolic blood pressure with the greatest reduction of 5-6 mmHg. In comparison to the active comparators, significant differences were observed in favor of Liraglutide in three out of four studies. We observed no significant differences in diastolic blood pressure, an average increase in heart rate of two to four beats per minute was observed. While no consistent treatment effects on plasma lipid levels were found, they tended to be a favorable trend on some parameters like triglycerides.

Based on this committee's recommendation from July 2008, FDA issued a guidance document on the assessment of cardiovascular risk for new anti-diabetic

therapies in December of 2008. Acknowledging that this was a program conducted before the guidance became available, we nevertheless were able to provide a meaningful evaluation of the major adverse cardiovascular events on MACE with Liraglutide.

I will start by summarizing the cardiovascular risk profile of our population before discussing the MACE analysis. This slide illustrates the percent of people with indicators of cardiovascular risk at baseline. Almost 20% were 65 years or older. More than 25% had diabetes duration of 10 years or more. More than 50% had hypertension, more than 50% had hyperlipidemia, more than 15% had overt cardiovascular disease and more than 25% had a reduced creatinine clearance. We consider this to be a representative sample of people with type 2 diabetes.

There are some inherent limitations in performing the cardiovascular MACE analysis on a data set from already completed clinical trials. It had to be performed retrospectively; no pre-planned adjudication could be performed. However, we looked at our MACE events and analyzed our data in a multitude of ways. This included different MACE definitions, different populations and comparators.

Furthermore, we also performed a post-hoc validation of our serious MACE events. In addition, the program gives a large randomized exposure experience including valuable data from the control extension studies. Therefore, despite the limitations, the MACE analysis provides an insight into the relative risk for cardiovascular events during Liraglutide treatment. Major adverse cardiovascular events are defined as cardiovascular death, nonfatal myocardial infarction or stroke. However, several approaches can be taken when defining these from a completed safety database. Based on an FDA request three definitions of adverse events that represented MACE were defined. These events were defined based on the standardized adverse event coding

system. Within the system families of adverse events are categorized together yielding a standardized approach towards which adverse events should be included in the MACE analysis.

Using this approach three definitions were used. An FDA list of adverse events called custom MACE being the narrowest subset of all three sets and two lists of adverse events designated SMQ narrow again being a subset of the broadest list of terms SMQ broad. We additionally subdivided this into not only looking at the total list of adverse events but also looked at those events meeting the regulatory definition of being serious. This specific terms included in these category can be found in the briefing document.

I will focus on the same two populations as also described in the FDA briefing document, being population A and B. Population A consists of people in the randomized control phase 2 and phase 3 trials up to the primary endpoint. This population is called population A2 in our briefing document. Population B includes all of those people in A plus those in the open label controlled extensions of the phase 2 and phase 3 studies. This population is called population B in our briefing document. It's important to note that the controlled extension patients in population B were maintained on their randomized therapy. So this provides an opportunity to accrue more events under controlled conditions and with longer exposure time.

This slide gives an overview of the exposure in each population in both the Liraglutide and combined comparator groups. On the left hand side, the number of subjects is shown with more than 4,000 patients included on Liraglutide. On the right-hand side the subject-years of exposure is shown with almost 3,000 patient-years of exposure on Liraglutide in population B.

Now let's look at the number of patients reporting a MACE event. All doses of Liraglutide have been combined and all controlled groups, placebo and active have been combined. From this we can make several important observations. If you look at the table from left to right then as the number of patients and patient years of exposure increases from population A to B, then the number of subjects experiencing an event also increases. When we look at the number of patients from top to bottom from the custom definitions to the broader definition then within each category, total or serious then the number of events also increases.

Further, when looking at the number of patients within each category, looking at the total MACE in comparison to the serious MACE groups. Then for the narrowest search custom there were fewer events. A larger fraction of these events was serious. This finding suggests higher specificity and lower sensitivity of this MACE definition. In contrast, the broader search had more events with a lower fraction being serious. This suggests higher sensitivity and lower specificity.

The incidence rates for MACE events across the population is shown here. Using the most specific MACE definition, the serious cases, we found an incidence rate of up to 1.5%. When discussing the comparator groups and which analysis to focus on, it's important that all subjects in long-term trials with diabetes were on glucose lowering therapy. We consider the total comparator group to be the most appropriate comparison from a cardiovascular risk perspective for the following three reasons.

Firstly, the separation between active and placebo comparator becomes artificial as this would mean that exactly the same therapy in one study would end in the placebo group and in another study in the active comparator group. Let we give true examples of that, the sulfonylurea group from the monotherapy study would be included

in the active comparator group, whereas in the SU combination study it would be included in the placebo group.

Similarly the metformin plus SU group from the 1572 study would be included in the active comparator group whereas the same treatment from the 1697 study would be included in the placebo group. Secondly, the fewer events there are, the less precise the estimated ratio will be. Thirdly, the estimate on confidence interval would be more sensitive towards differences in statistical approach. Therefore, I will focus on presenting the total Liraglutide versus total comparator analysis but will also provide an overview of the results from the comparison to placebo and active comparator groups separately.

Using a statistical analysis stratified by trial we estimated the incidence ratios in 95% confidence intervals. On this slide we have included the MACE analysis in the true populations for all adverse events using the three MACE definitions. The data presented is for total Liraglutide versus total comparator. The total number of subjects in each analysis is also presented. Regardless of the broadness of terms that were applied, all the population, there was a general agreement and consistency on both the point estimates and confidence intervals. All of the estimated incidence ratios were less than one and all of the over 95% confidence intervals were less than 1.8. When we look at MACE events reported as serious, thus with a higher level of specificity, we reach the same conclusion.

Regardless of the broadness of terms that were applied, all the population, there was a general agreement on the point estimates and confidence intervals. Again all of the estimated incidence ratios were less than one and all of the upper 95% confidence intervals were less than 1.8. This slide tabulates the point estimates on the left-hand side

and the upper 95% confidence intervals on the right-hand side for placebo and active comparator separately and the total comparator combined for total MACE events. Looking only at the placebo comparison then the point estimates are around 1 as seen in the left. The over 95% confidence intervals are above 1.8 on the right. For the active comparator comparison all point estimates remain less than one and all upper 95% confidence intervals are less than 1.8. However, as mentioned earlier, the fewer events the wider the estimate becomes and this is most apparent in the placebo comparison.

We performed a number of additional sensitivity analysis to pressure test the validity of our conclusions. While no prospective and formal blinded adjudication of the events could be performed, Dr. Steven Marso from the Mid American Heart Institute performed an assessment of the validity of the diagnosis of our MACE events reported as serious. This was done without knowing the randomized treatment of the individual cases.

Based on this evaluation five cases out of the total 44 serious brought MACE events were evaluated as not being MACE events. With the remaining events being rated as definite or probable events. We re-ran our MACE analysis excluding these five cases and as shown here boxed in yellow, we still found that all of the estimated incidence ratios were less than one and all of the upper 95% confidence intervals were less than 1.8.

Additionally one study in the development program compared the effect of Liraglutide to rosiglitazone on an SU combination background study 1436. Since rosiglitazone may be associated with an impaired cardiovascular outcome, we looked into the MACE events in that study and found that the rosiglitazone did not contribute with

any serious MACE events in any MACE definition. Only in the broad SMQ definition, five events were found in the rosiglitazone arm.

I am here presenting the MACE analysis with and without the rosiglitazone arm from the 1436 study. This did not affect our MACE conclusions. Acknowledging the mentioned limitation, the MACE analysis nevertheless provides a meaningful and robust insight into the relative risk for cardiovascular events with Liraglutide. We studied a representative sample of people with type 2 diabetes and in our population the incident rate of serous MACE events was up to 1.5%.

The MACE analysis findings were consistent across a number of different populations and MACE outcome definitions including various sensitivity analysis. In the largest data set with most events accrued, total Liraglutide versus total control, all of the estimated incidence ratios were less than one and all of the upper 95% confidence intervals were also less than 1.8. This was also the case for those MACE events meeting the regulatory definition of being serious. With that, I would like to thank you for your attention and Dr. Alan Moses will now present the benefit risk and risk management plan for Liraglutide.

LIRAGLUTIDE BENEFIT/RISK AND RISK MANAGEMENT PLAN

ALAN C. MOSES, M.D.

Thank you, Milan. Novo Nordisk believes that Liraglutide offers a substantial advance in the management of type 2 diabetes. It effectively lowers and sustains glucose levels. With a 1% to 1.5% reduction in HbA1c. It brings a high percentage of patients to recommended target levels of Hemoglobin A1c. Importantly it also decreases weight, improves beta cell function and is associated with a low rate of hypoglycemia. All of these attributes differentiated from many currently available

treatments. Liraglutide's once daily administration makes this drug easy for patients to use. We believe that the strong benefit risk profile of Liraglutide is strongly in favor of it's clinical benefit. Let's go through the potential areas of concern, one by one and summarize why we believe that they have been or will be addressed.

During the Liraglutide development program, one specific pre-clinical finding, a signal of C-cell changes in rodents, led to an extensive investigation of the mechanisms behind these changes and resulted in an extensive clinical monitoring program. We have detailed why we believe that the mechanisms underlying C-cell changes in rodents do not pertain to non-human primates or to man.

Calcitonin is a valid biomarker of C-cell activation. In studies of more than 5000 people, we found no clear drug dependent evidence of C-cell activation. Specifically, there was no evidence for time dependent or exposure dependent increase in calcitonin levels in patients exposed to Liraglutide relative to active comparators. The identification of several patients with incidental papillary carcinomas of the thyroid was a direct result of the intensive calcitonin and thyroid screening program as you have heard from Dr. Daniels.

Pancreatitis has been identified as a potential risk with GLP-1 receptor agonist. In the Liraglutide development program we identified a small number of cases of acute pancreatitis. The rate of pancreatitis was not greater than that reported in the population of patients with type 2 diabetes. We will continue to monitor for these events in both the ongoing trials and in post-marketing outcome studies.

Turning to Liraglutide's cardiovascular profile. In the human physiologic studies there was no evidence of QT prolongation induced by Liraglutide. There were no adverse effects on traditional biomarkers of cardiovascular risk including blood pressure,

which was lowered. I would like to reiterate Novo Nordisk's commitment to cardiovascular safety. We have submitted a synopsis to the FDA for a post-approval cardiovascular study that will follow the approach outlined in the current FDA guidance and about which we are anxious to engage the FDA in further discussion.

You have heard in Dr. Zdravkovie's presentation the outcomes from a number of MACE analyses that we conducted based on specific criteria requested by the FDA on data from the comprehensive Liraglutide development program. The analyses presented today focused on the populations reviewed by the FDA in their briefing document. These analyses consistently revealed the point estimate for the hazard ratio of MACE events of 1.0 or less and an upper bound of the 95% confidence interval consistently less than 1.8.

We believe that the aggregate pre-clinical, physiologic and clinical data are consistent with approval of Liraglutide from a cardiovascular safety perspective while requiring a post approval study to definitively rule out a hazard ratio of greater than 1.3. An important component of our ongoing safety assessment of Liraglutide is built into the current ongoing phase 3b program for Liraglutide in some 1800 additional patients with diabetes.

These individuals have been enrolled into a trial comparing Liraglutide to exenatide that already has been completed into a study comparing Liraglutide to the DPP-4 inhibitor sitagliptin and into a trial that recently began enrolling that evaluates Liraglutide in combination with the basal insulin Levemir. In addition, we will be conducting a pharmacokinetic study in patients aged 10 to 17 and a safety and efficacy study in the same aged pediatric population.

These studies allow for a collection of additional safety assessments in blinded randomized studies. We have developed a proactive comprehensive risk management plan for Liraglutide that includes continuing and structured risk assessment. We will utilize three elements in our approach. The first is effective, clear labeling. The second is post-marketing pharmacovigilance and the third is through post-approval study commitments that I will describe in just a moment.

In addition to appropriate safety updates to the label, we will employ two approaches to pharmacovigilance. One, we will use the errors database to assess spontaneous reports of adverse events. While we have not yet submitted the next proposal to the FDA we are in active discussion to conduct a proactive large prospective claim safety surveillance database study applying the i3 Aperio system. This system will assess any infrequent or rare signals that were not detected in the phase 3 development program. We will compare the effects of Liraglutide to the effects of other standard diabetes therapies with a focus on thyroid and C-cells, on cardiovascular events, and on pancreatitis. Data will be reported to regulatory authorities at regular intervals for the next three to five years.

Finally, let me turn to our plans for a large prospective cardiovascular outcome clinical trial. The post-approval cardiovascular outcome study will be randomized and controlled and will be designed to assure the statistical power to definitively rule out excess cardiovascular risk with Liraglutide. We will enroll 9000+ patients at moderate to high risk of cardiovascular events, randomizing them either to receive placebo or Liraglutide on a background of standard diabetes therapy.

These patients will be exposed to therapy for a minimum of 3½ years, making the overall trial 5 years in duration or until sufficient events have occurred to

achieve the primary endpoint. There will be an international expert advisory committee for this trial. An independent data safety monitoring committee will monitor all cardiovascular events based on data provided by an independent event adjudication committee.

The DSMB will conduct ongoing safety analyses and defined stopping rules will be applied. This will be an event driven trial. It will seek sufficient total MACE events to achieve a primary endpoint to exclude an excess cardiovascular risk of cardiovascular death, nonfatal MI or nonfatal stroke at a relative risk level of greater than 1.3. We also will have the opportunity to assess additional safety endpoints.

In conclusion, we believe that Liraglutide provides important clinical attributes as a new treatment for type 2 Diabetes. These attributes distinguish it from currently utilized therapy and address the multiple abnormalities that characterize type 2 diabetes. Liraglutide met its primary regulatory endpoints for glycemia control in the treatment of type 2 diabetes by very substantially reducing A1c. It did this by rapidly decreasing both fasting and postprandial glucose levels and sustaining these decreases over time.

The development program was designed to directly compare Liraglutide to current treatment approaches to type 2 diabetes. Liraglutide generally produced superior efficacy compared to these standard therapies. As outlined in the recently revised ADA/EASD treatment algorithm as discussed by Dr. Buse, Liraglutide also demonstrated other favorable characteristics including weight loss, improved beta cell function and ease of use by the patient. In the absence of concomitant use of sulfonylureas it was associated with a very low risk of hypoglycemia.

There is a real need for new and innovative treatments of type 2 diabetes that achieve therapeutic goals and provide simplicity and convenience for the patient. We believe that Liraglutide is such an innovative therapy. Based on its glycemic efficacy and its positive effects on non-glycemic parameters in diabetes important to patients we conclude and hope that you agree that the benefit risk profile is highly favorable for Liraglutide and that you will support its approval in the treatment of type 2 diabetes.

Thank you for your attention. With the Chair's permission I am going to move to the other microphone, is that all right Dr. Burman?

CLARIFYING QUESTIONS FROM THE

COMMITTEE TO SPONSOR

DR. BURMAN: Thank you, Dr. Moses, yes. I would like to open the floor for discussion and questions specifically to the Sponsors. It's about 9:40 or a little after and we will go until 10 o'clock. I have lots of questions myself that I will save but I did want to just bring up two quick points. Dr. Daniels had mentioned that the American Thyroid Association did not recommend measuring calcitonin levels universally for universal screening, but an equally prestigious organization, the European Thyroid Association has. Number two, I just wanted to mention that it's controversial regarding the increased incidence of thyroid cancer, is it only due to detection or is it related to some change in biologic activity of thyroid cancer? In fact the mortality rate of thyroid cancer in man is increasing extremely fast rate. Just this two general comments, Dr. Daniels do you want to?

DR. DANIELS: Yes. Although the European Endocrine groups have recommended calcitonin screening, a recent paper published within the last few months

by five or six of the leading European medullary thyroid carcinoma experts including Dr. Martin Schlumberger have concluded that there is really no compelling evidence for a benefit of calcitonin screening in this population and that this does need further investigation. So although some European organizations have recommended this, there are problems and specifically some of the problems include the fact that nobody really knows what the consequences of finding medullary microcarcinomas are and people are so used to the devastating consequences of overt medullary carcinoma that they tend to think when they find a small microscopic medullary carcinoma, that all of those are going to grow into macroscopic medullary cancer and that's clearly not known. So the American Thyroid Association did not recommend this and some of the leading European experts reanalyzing all of this data came to the conclusion that screening might not be indicated.

DR. BURMAN: That's fine. You had one other quick comment?

DR. DANIELS: I was going to comment on your second question or do you want to ask me something further about that?

DR. BURMAN: No why don't we just ask for discussion of the committee. Did you have a quick comment on that? On my second part?

DR. DANIELS: Yeah. Although there is an increase in the mortality in men, if you actually look at the numbers they are actually very, very small numbers with a little bit of blip over time. It's very hard to tell whether that's a true difference, and in fact since men have about two-thirds the number of thyroid cancers as women, if you were to just do all kinds of screening, clinically men tend not to be diagnosed unless the cancers get to be rather large. So in men if you are finding larger cancers then the mortality may be somewhat greater.

DR. BURMAN: Thank you. I would like to open it up to Dr. Felner.

DR. FELNER: Yeah. You were able to show that the GLP-1 receptor is localized in the C-cells of the rats and you know that there is activation of calcitonin in the rats and you said there was no activation in humans or in non human primates. Were you able to know if, or determine if, GLP-1, if human C-cells or follicular cells actually carry the GLP-1 receptor? Do you know that?

DR. MOSES: Yes, let me turn to Dr. Lars Madsen from our pre-clinical group to answer that question.

DR. MADSEN: Thank you. Lars Madsen, pre-clinical. I think the important thing is that we have looked by a variety of techniques and we have consistently demonstrated there is a species difference. So, summarizing those techniques, what was already shown in the core presentation was that we used immunohistochemistry and were able to localize the receptor on the C-cells, we also used in situ hybridization with similar results and in addition we have recently reproduced literature results using in situ ligand binding.

If we are summarizing across species for these, as you can see by the immunohistochemistry method, which is not identifying whether functional protein is present, we can identify the protein in all species tested. However, when we use other techniques such as in situ ligand binding and in situ hybridization, we see that only the mouse and the rat express the receptor and with RT-PCR we see a moderately lower receptor expression in humans than in rodents.

So based on this, we conclude that there is marked species difference in the receptor expression level and most importantly based on the functional data we conclude that there is no evidence of functional effect of GLP-1 receptor in humans.

DR. BURMAN: Thank you. Marvin.

DR. KONSTAM: Well maybe we could dwell on that for a couple of minutes and have some of our other experts comment on it because, you know, so what I am getting out of that is in fact, you know, by immunohistochemical studies the GLP-1 receptor is present in humans and so you don't have much in terms of the biologic assay that's I guess granted. Then there was another question about so maybe, you know, I would like to hear more about that.

DR. TUTTLE: Show that slide again, the one that just came up. What you are showing is that you find GLP receptor protein and messenger in thyroid tissue, the question is on your immunohistochemistry are these in the C-cells or can you localize to anywhere in the thyroid?

DR. MADSEN: With the immunohistochemistry we are quite confident that the expression is localized solely on the C-cell. Similarly, with the in situ ligand binding we see an overall core localization of the C-cells being GLP-1 receptor positive. I agree when we come to the RT-PCR basically what you identify is not related to a new specific cell type. The consistency of the results show that there is a mildly lower receptor expression in the primate species and as already mentioned this correlates with the lack of a functional response.

DR. BURMAN: Thank you. Dr. Teerlink.

DR. TEERLINK: So, just to clarify, so you were saying that in terms of humans there is – if you could just leave that slide up, that there is, is there GLP-1 receptor in human C-cells? Secondly, we see that there is not good binding of GLP-1 there, but have you ever tested whether there is Liraglutide binding?

DR. MADSEN: Excuse me, what was the last one?

DR. TEERLINK: The second thing is, have you tested for Liraglutide binding to these human receptors? Because you have created a different protein, it might have different binding characteristics to where GLP-1 may not bind but the Liraglutide may.

DR. MADSEN: Right. To address your first question regarding the presence of the receptor in human C-cells, we have tested this again by the immunohistochemical method and the picture I show you here are from normal human thyroid where we have positively identified the GLP-1 receptor positive cells as being C-cells and that the follicular cells of GLP-1 receptor are negative. We also extended this study to include a number of follicular adenomas and carcinomas from surgery specimens and again the results were completely consistent that expression of GLP-1 receptor was confined to the C-cells.

DR. BURMAN: A point of clarification, the title seems misleading. It says no GLP-1 receptor in human thyroid and what you mean is no GLP-1 receptor in follicular cells but it is present in C-cells.

DR. MADSEN: I'm sorry. I'm sorry.

DR. BURMAN: Yeah, good.

DR. TEERLINK: Was there any evidence of the Liraglutide? Have you ever tested Liraglutide binding to human C-cells?

DR. MADSEN: It's very complicated to test Liraglutide on tissue samples due to the high affinity for protein binding. So the in situ ligand binding and radiolabeled ligand binding studies that we have performed have been focused on using either native GLP-1 or extended based analogues of GLP-1.

DR. TEERLINK: So you have hypothesized that there are differences in receptors between species and these might have different properties. You are also hypothesizing that you are now introducing a different protein which may or may not have different binding characteristics to different receptors. Is that an appropriate summary of that?

DR. MADSEN: I think the most appropriate comparison of the different GLP-1 receptor agonist and their action in C-cells is what we already shared with you in the core presentation. That is, in cell lines we have a very consistent response both with regard to C-cell activation measured as CAMP and also with regard to calcitonin release when we test rat C-cell lines. So I think we have convincingly demonstrated that this is a GLP-1 receptor mediated effect and also the in vivo data support this. Based on the absence of a similar signal in the human data, both in vitro and in vivo, we conclude that this is not of human relevance.

DR. BURMAN: If I might, you only used, what cell line did you use for the calcitonin stimulation on humans, was it the TT-cell line?

DR.MADISON: That is correct

DR. BURMAN: That's only one line that's been around a long time. It's hard to know the characteristics of that line. Did you test in vitro human thyroids cells taken freshly from human patients?

DR. MADSEN: There are two technical challenges to that specific technique. The one being obtaining the fresh thyroid tissue. That’s of course circumventable. The other one being, which we have tested out in mice and rats, the signal to noise ratio if you do ex vivo ligand binding and stimulation. We were not able

to achieve a successful signal to noise ratio in rodents so we did not pursue this in human thyroid samples.

DR. BURMAN: Thank you. Dr. Tuttle.

DR. TUTTLE: You had shown that you looked at GLP-1 receptor state. You have shown that the follicular adenomas and the thyroid cancers derived from follicular cells do not have GLP-1. I assume you have looked at medullary carcinoma as well? Do they have it as increased density, less/more than the normal C-cell?

DR. MADSEN: Yes. So I guess it's also referenced in the FDA briefing book that has actually a paper looking specifically at this using in situ ligand binding or auto radiography as is also mentioned. This, as I said, is the kernel publication and it has tested a number of different tumors and what we can see is that there are certain tumors that have level of expression but the level of expression in the medullary thyroid is limited to only a subset of tumors and the same paper also showed that when you look at the normal tissue in humans there is only a very limited number of normal human tissues from samples which expressed the receptor.

DR. BURMAN: Thank you. Are there any other questions from the rest of the group?

(No response.)

I would like to ask another one, if I may, we have a few minutes. You said that that there was no evidence of Liraglutide increasing C-cell activation or hyperplasia in humans but (I am looking at slide CE-53) there is unstimulated basal calcitonin levels that appeared to go up in the Liraglutide treated groups compared to placebo or active comparator (depending on the time) and then gradually filtered back

down over week 104. I think those values were statistically significant compared to baseline. Doesn't that indicate that there is an effect of Liraglutide on C-cells?

DR. MOSES: I agree, Dr. Burman, that there is a slight statistical increase in the percent increase. I think we also have to look at what this means within the range of calcitonin being measured, which is actually less than one picogram per mL. (If we could go to CE-52 please). Just as a reminder, from a clinical perspective these are the data from the 24-month studies so we have patients now, these data are from the longitudinal studies for individuals who had been in study for full 24 months. I think you can see, as Dr. Zdravkovic has already pointed out, in the inset of the top that there is a little bit of variation of calcitonin levels over time within this assay and over time. There is no relationship to either dose of Liraglutide or difference between Liraglutide and active comparator. So we believe that there is in fact no consistent or interpretable pattern that would suggest that Liraglutide increases calcitonin release.

DR. BURMAN: Dr. Tuttle.

DR. TUTTLE: How do you balance for me that same CE-52 slide with CE-59? CE-59 is the obesity study?

DR. MOSES: Yes.

DR. TUTTLE: Where at 26 and 52 weeks and the other study we are seeing a flat even calcitonin. This is continually going down, what's the difference?

DR. MOSES: I'm not sure I can explain the difference CE-59 please on. This is the slide that Dr. Tuttle is referring to and this is again from the obesity study. Again, a study with higher doses of Liraglutide which if anything should accentuate a response if there is going to be a response. I actually believe that we are dealing with issues at the lower end of assay function.

The lower limit of detection of the assay is 0.7, that's been validated. It's a highly specific, highly sensitive two antibody immunoassay. We are dealing with levels that are in the one picogram/mL range and I quite frankly from a clinical perspective have no clear way of interpreting this. Particularly since it varies in trial to trial in terms of the exact pattern but they never get over one picogram/mL. So my interpretation of this is that from a clinical perspective and from a perspective of actually demonstrating activation of C-cells by Liraglutide we just have no data, no convincing data, that it does so.

DR. BURMAN: We have really about 2 minutes. Marvin, do you have a quick question and...

DR. KONSTAM: Are we going to have more time to question them later? There is a lot of things that I would like to ask.

DR. BURMAN: Sure, we are going to have more time in the afternoon.

DR. KONSTAM: Well let me just follow up on this and maybe our other thyroid experts can comment on this. So it seems as though, at least in the early going, there is an increase over baseline. I look at slide CE-53 and although very modest, admittedly, at week 12 and week 26 there seems to be some dose response to that increase. The FDA focuses on this.

I am struggling with your comment that this is not clinically relevant because the whole reason we are focusing on this as a potential biomarker for GLP-1 activation in the thyroid and I am wondering, you know, you showed medullary carcinoma samples where a few of them were GLP-1 positive. It's a rare tumor to begin with, I am not sure how you can look at the increase that is there and say, you know, it's not clinically relevant. I don't know what clinically relevant is.

DR. TUTTLE: Let me turn to Dr. Daniels who I think can probably explain clinical relevance better than I.

DR. DANIELS: I think, it's fair to say that calcitonins in this range would be considered by thyroid experts. I think I could probably speak for Dr. Tuttle and Dr. Burman. They are not relevant at all in this range and until the calcitonin gets to at least ten and usually over 20, we don't even pay attention to it. The problem with calcitonin measurements is that there are, there is a great deal of noise, the co-efficient variation of the assay is very high. There has been a suggestion about whether glucose control actually has an influence on calcitonin concentrations, but I would contest that no thyroidologist would pay attention to calcitonin variations in this range as having clinical significance.

DR. BURMAN: We're going to take a break in one second. Mike, do you agree or disagree with that comment?

DR. TUTTLE: Yeah, I agree. To me, these shorter levels of calcitonin are the difference between a creatinine of 0.6 and 0.7 where you may see statistical change but little clinical significance. Over time we generally do not worry about calcitonin until they get above 30, 40 or 50. Even as they showed you, it is hardly ever medullary until you are above 100. So what I am trying to figure out is whether there really is a trend here. The other thing I am trying to figure out is whether we have some co-factor going on that we are not measuring that is different in these studies; it's their weight, it's their proton plump inhibitors, it's all of things that affect calcitonin if these studies were not designed to measure that could be different between the groups.

DR. MOSES: Dr. Tuttle, you do raise one important issue and that is concomitant use of H2 blockers and PPIs which did turn out to be higher in the

Liraglutide group perhaps because of some of the GI side effects that will introduce. Now, whether that's the explanation for this or not, I don't know. As Dr. Daniels also suggested, there are data in the literature that suggests that improved glycemia control can also affect calcitonin. So I think we really do not know or have a definitive answer to that question.

DR. BURMAN: Thank you both. Try to stay on schedule because this is going to be a very busy afternoon as well. We will now take a 15-minute break, panel members please remember there should be no discussion of the meeting topic during the break among yourselves or with other members of the audience, we will resume at 10:15.

(Morning break.)

DR. TRAN: Please take your seat. We will start in a moment, thank you.

DR. BURMAN: All right, why don't we restart? We will now proceed with our presentations from the FDA. 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. Dr. Anthony Parola from the FDA will be presenting.

FDA PRESENTATION PHARMACOLOGY-TOXICOLOGY

ANTHONY PAROLA, PH.D.

Good morning, Chairman Members of the Advisory Committee, ladies and gentlemen. Thanks for the opportunity to present Non-Clinical Safety Findings for Liraglutide injection, a GLP-1 receptor peptide agonist, being developed by Nova Nordisk for the treatment of Type 2 diabetes. After my presentation, Dr. Karen Mahoney and Dr. Janice Derr will address clinical cardiac and thyroid safety findings. My presentation will focus on thyroid C-cell tumors that occurred in two-year lifetime

exposure Rodent Carcinogenicity Studies of Liraglutide and evaluation of the human relevance of rodent tumors, in an effort to determine human relevance, the applicant proposed a mode of action for Liraglutide induced rodent C-cell tumors. The mode of action was evaluated in an extensive series of mechanistic studies including studies in mice, rats and monkeys. I will discuss interpretation of those mechanistic studies with an emphasis on results that do not support mode of action.

DR. BURMAN: Dr. Parola, can I interrupt just for one second, I apologize, can people in the back hear him, please speak into the microphone a little more, thank you.

DR. PAROLA: In the last part of my presentation I will discuss the relevance of rodent C-cell tumors to human risk. Thyroid C-cell tumors occurred in Carcinogenicity Studies of Liraglutide in mice and rats. Animals were injected subcutaneously once a day, because that's the intended clinical route and frequency of drug administration. Selected doses yielded plasma drug levels below clinical exposure at low doses at larger multiples of human exposure at high doses. Higher doses were included to maximize the potential to detect-drug induced tumorigenicity in products intended for chronic use.

Tissues were examined microscopically after animals were sacrificed at the end of the study or if the animals died during the study. Tissue samples including thyroid were examined by standard staining techniques, Liraglutide cause thyroid C-cell tumors in both sexes of rats and mice at clinically relevant exposures. In high dose male mice, Liraglutide cause fibrosarcomas on the dorsal skin and subcutis, the body surface used for drug injection at high multiples of human exposure. Although the Sponsor

associates these dorsal surface tumors with injection sites or implanted microchips or analysis attributes them to treatment.

This table summarizes thyroid C-cell tumor findings in rats. Liraglutide doses of 0.075, 0.25 and 0.75 yielded multiples of human exposure ranging from less than clinical exposure at the low dose to eight times clinical exposure at the high dose. Human exposure multiples are based on comparison between rat and human plasma exposure over a 24-hour period at the maximum proposed clinical dose of 1.8 milligrams per day. The incidents of C-cell findings are expressed as percentages, an asterisk indicates the incident was statistically significantly different from controls; underlined values were above concurrent controls and above historical control group values from two years studies at the same testing facility.

Liraglutide dose dependently increased the incidents of benign adenomas, malignant carcinomas and total C-cell tumors at low multiples of human exposure in both male and female rats. Focal C-Cell hyperplasia, a precursor to tumors, also occurred at low multiples of human exposure in both sexes. This table summarizes thyroid C-cell findings in mice, Liraglutide doses of 0.03, 0.2, 1 and 3 milligrams per kilogram yielded multiples of human exposure ranging from 0.2 at the low dose to 45 at the high dose.

Liraglutide dose dependently increased the incidents of benign adenomas in males and females and because it caused a low incidence of malignant carcinomas in high dose females, it also increased the incidents of total C-cell tumors in females. Focal C-cell hyperplasia also occurred at low multiples of human exposure in both sexes. To summarize, Liraglutide is non-genotoxic and it cause thyroid C-cell tumors in male and female mice and rats in two years studies. C-cell tumors occurred at low multiples of human exposure in both species. In rats, malignant C-cell carcinomas occurred in males

and females at clinical relevant exposures, but in mice, carcinomas only occurred at high multiples of human exposure in high dose females.

There are species differences in spontaneous incidents of proliferative C-cell lesions and these findings are summarized in this table. Rats and mice differ in their propensity to spontaneously develop C-cell hyperplasia and tumors. C-cell proliferation is better characterized in rats than in mice, because diffuse hyperplasia, focal hyperplasia and adenomas are common in rats and their incidents increases with age. The background incidents of malignant C-cell carcinomas in rats is low. Proliferative C-cell lesions are rare in mice and they are rare in humans. C-cell carcinomas are rare except in humans with Familial Medullary Thyroid Carcinoma or MTC. Activating mutations in the re-arranged during transfection protooncogene or RET protooncogene cause Familial MTC, because the progression or proliferative lesions in rats and human Familial MTC is similar with C-cell hyperplasia progressing to tumors, rats were considered a model for the human disease. However, the molecular pathology of Familial MTC activating mutation in the RET proto-oncogene have not been established in rats. A few marketed drugs caused thyroid C-cell tumors in rats.

This table summarizes C-cell tumor findings in rats and mice for approved drugs and Liraglutide. Seven approved drugs in seven different pharmacologic classes, that caused thyroid C-cell tumors in rats, were identified by searching label information in drug Facts & Comparisons. Human exposure multiples at the lowest dose or exposure causing C-cell tumors in rodents are shown for each drug. Most approved drugs only cause benign adenomas in rats, usually in one sex and usually at high multiples of human exposure. In contrast, Liraglutide causes C-cell tumors in both male and female rats and

mice at low multiples of human exposure. Liraglutide increases the incidents of malignant C-cell carcinoma in both rats and mice.

Exenatide, an approved GLP-1 agonist with a shorter duration of action, caused benign adenomas in female rats only; no approved drug causes C-cell tumors in mice. Spontaneous and drug induced C-cell tumors in mice are rare. Until recently, Liraglutide was unique, because it was the only known investigational or approved drug causing C-cell tumors in both rats and mice at clinically relevant exposures. Mechanistic studies performed by Nova Nordisk using sustained release Exenatide and recent results from repeat dose toxicity studies and preliminary results from Carcinogenicity Studies using long acting GLP-1 agonists, show focal hyperplasia in C-cell tumors in rats and mice are probably a pharmacologic class effect of long acting agonist. Nova Nordisk proposed a mode of action for Liraglutide induced thyroid C-cell tumors in rodents, and then evaluated it in an extensive series of mechanistic studies, with the goal of determining the human relevance of rodent tumors.

The schematic of the proposed mode of action is shown on this slide, I will note that this was the mode of action submitted in the NDA and it's the one I evaluated. GLP-1 receptor agonist activate GLP-1 receptors on thyroid C-cells causing increased Calcitonin secretion and synthesis, Calcitonin is a hormone secreted from the thyroid in response to increased blood calcium, Calcitonin lowers blood calcium primarily by inhibiting osteoplast-mediated bone resorption.

Persistent Calcitonin secretion and synthesis leads to C-cell hyperplasia and hyperplasia progresses to Neoplasia, C-cell hyperplasia in rodents can be either diffuse or focal, and we agree that focal C-cell hyperplasia may progress to C-cell Neoplasms. We do not agree that Plasma Calcitonin is a pre-hyperplasia biomarker.

Plasma Calcitonin can be increased by increasing regulated secretion but it can also increase with C-cell mass. Calcitonin is being used as a biomarker for hyperplasia in clinical studies of Liraglutide. This mode of action proposes that persistent Calcitonin secretion and Synthesis drives hyperplasia, but this has not been demonstrated for any other drug and Liraglutide does not cause diffuse hyperplasia considered a physiologic response, but only causes focal hyperplasia, which is a precursor to tumors in rodents.

Although Liraglutide increases Calcitonin in mice, it has no durable effect on plasma Calcitonin in rats therefore there is no evidence increased Calcitonin secretion and synthesis drive C-cell hyperplasia in rats. Pharmacologic class effects linking increased Calcitonin secretion to C-cell tumors has not been established for any approved drug causing C-cell tumors in rats, Cinacalcet, a Calcitonin secretagogue in rats does not cause C-cell tumors in mice or rats. Cinacalcet is a calcium sensing receptor agonist that only transiently elevates plasma Calcitonin due to counter regulatory effects of Calcitonin on it's own secretion.

Calcitonin secretion is regulated by extracellular calcium with high levels of calcium increasing secretion by activating the calcium sensing receptor on C-cells. Calcitonin inhabits osteoclast mediated bone resorption lowering blood calcium. The resulting hypocalcemia decreases Calcitonin secretion. This negative feedback inhibits persistent Calcitonin release. Cinacalcet increases calcium sensing receptor sensitivity to calcium and increases Calcitonin secretion, but its effects are mitigated by negative feedback, other hormones including gastrin CCK glucagon and probably GLP-1 increase cyclic AMP depended calcium induced Calcitonin secretion.

Although Cinacalcet increases Calcitonin, its effect is transient because of negative feedback. Cinacalcet does not cause C-cell tumors in rats or mice and actually

significantly decreased the background incidence of benign adenomas in male rats in a two-year Carcinogenicity study.

The table on the right summarizes proliferative C-cell findings in male rats from the two year study of Cinacalcet, adenomas were significantly decreased in mid and high dose groups. Although Cinacalcet increases Calcitonin secretion, its effect is transient because of negative feedback. GLP-1 increases Calcitonin secretion from perfused rat thyroid and the effect is Calcitonin is calcium dependent. GLP-1 effects on plasma Calcitonin in vivo are not well characterized. The two graphs on the right show the effects of GLP-1 on Calcitonin released from perfused rat thyroid in the presence of low calcium; figure A on top and in the presence of high calcium, figure C below. The top figure shows that at low calcium concentrations, GLP-10 animal or GLP-1 had no effect on Calcitonin secretion, the bottom figure shows one in ten animals are GLP-1 dosed dependently increased Calcitonin secretion above the level elicited by 3 millimolar calcium alone. GLP-1 induced Calcitonin secretion is calcium dependent in rats. The effect of GLP-1 on Calcitonin release may be similar to its effects on insulin secretion in that it increases the amount of hormone secreted by high levels of the physiologic stimulus, but doesn't have an effect at lower levels.

The proposed mode of action does not account for calcium dependence of GLP-1 receptor mediated Calcitonin secretion or negative feedback that would otherwise inhabit persistent secretion. Liraglutide does not cause those dependent durable elevations in plasma Calcitonin in rats. In rats and mice, Liraglutide does not cause hypocalcemia. The proposed mode of action does not account for regulatory effects on Liraglutide stimulated Calcitonin secretion, therefore the mechanism of persistent Calcitonin secretion, when it occurs is not known. There were no sustained measurable

effects of hyper Calcitonin anemia in Liraglutide treated mice or rats and hypocalcemia didn't occur. Other parameters of Calcitonin activity were not measured including bone mineral density, bone mineral content or biomarkers of osteoclast activity.

Human relevance of the proposed mode of action depends on differences between humans and rodents and thyroid C-cell GLP-1 receptor coupling to Calcitonin secretion and synthesis. Our analysis of Liraglutide's effect on Calcitonin synthesis concluded it increased thyroid Calcitonin MRNA in mice but not in rats. Because human thyroid Calcitonin MRNA couldn't be assessed, I will focus on Liraglutide's effect on plasma Calcitonin later on. The Sponsor performed immunohistic chemical and In Situ Hybridizations Studies in thyroid and extensive characterization of GLP-1 receptor coupling to Calcitonin secretion in rat and human C-cell lines, attempting to demonstrate species differences in receptor cell localization and Effector Coupling. Results from these studies are not sufficient to conclude for a species differences in either cell localization of GLP-1 receptors or that any difference is occurring in receptor mediated Calcitonin secretion in C-cell lines are relevant in vivo.

GLP-1 receptors are current thyroid from mice, rats and humans, but aside their localization was not determined. This table summarized the results from key studies aimed at localizing GLP-1 receptors to C-cells. A published autoradiographic ligand binding study showed thyroid from 60% of mice, 100% of rats and 6% of humans were GLP-1 receptor positive; 28% of human medullary thyroid carcinomas, which are derived from C-cells were also receptor positive.

GLP-1 receptors occur in thyroid of all rats and in sub-populations of mice and humans. Receptor expression is more common in human C-cell tumors than in normal thyroid. Immunohistochemical staining and in situ hybridization studies

evaluating receptor protein expression in MRNA levels in thyroid performed by Nova Nordisk were inconclusive due to technical problems. GLP-1 Receptor Ligand Binding studies in rat and human C-cells lines showed two rats cell lines were receptor positive and a human cell line was not. Receptor coupling to Calcitonin secretion was evaluated in rat and human C-cell lines, the graph on the left shows GLP-1 agonist, including Liraglutide dose dependently elicit Calcitonin secretion from rat MTC 6-23 cells. The graph on the right shows the same agonist did not cause Calcitonin secretion from human TT cells, even though basal Calcitonin release is about 50 fold higher in the human C-cell line.

C-cell lines cannot be used as the basis for species differences in GLP-1 receptor coupling to Calcitonin release, receptor expression and coupling in cell lines may be different from normal C-cells in vivo and may depend on culture conditions. Pentagastrin a potent Calcitonin secretagogue in humans didn't elicit Calcitonin secretion from human TT cells. Glucagon elicits Calcitonin secretion from rats CA-77 cells, but in one study, not from MTC 6-23 cells. Furthermore, not all human C-cell lines would be expected to be GLP-1 receptor positive, because only 28% of human medullary thyroid carcinomas were positive in an autoradiographic ligand binding study.

Increased Calcitonin secretion from C-cells raises plasma Calcitonin levels. There are discrepancies between the effects of Liraglutide and plasma Calcitonin and the proposed mode of action in which drug-induced increase Calcitonin secretion drives hyperplasia and Neoplasia. In a mechanistic study, Liraglutide was administered subcutaneously once a day to male rats using the same doses as those used in the Carcinogenicity Study. Rats were treated for up to 69 weeks with plasma Calcitonin measured throughout the study.

This histogram shows plasma Calcitonin versus Liraglutide dose at different times during the study on day one and in week 17 and in week 43. Results from the control group show that there was a large increase in Calcitonin between day one and week 17 and further increase between week 17 and week 43. Calcitonin levels in Liraglutide treated groups were similar in the control group for all sample times. Plasma Calcitonin was not Liraglutide dose or treatment duration dependent in rats. It's important to note that Liraglutide did not cause any sustained dose related increase in plasma Calcitonin prior to causing proliferative C-cell lesions. In the high dose group, Liraglutide had no effect on focal C-cell hyperplasia or adenomas in week 17, but increased the incidence in both in week 43. There was no difference in plasma Calcitonin between control and high dose groups in week 43 therefore Calcitonin was not a biomarker for C-cell focal hyperplasia or tumors in rats. Unlike rats and mice, Liraglutide does dependably increase plasma Calcitonin after the first dose and the effect was durable.

Calcitonin was measured in weeks 26, 52 and 104 in the two year mice Carcinogenicity study. Calcitonin increased at doses of 0.2 milligrams per kilograms Liraglutide and above; the same doses causing C-cell hyperplasia or tumors. The graph on the left shows Calcitonin increased with both Liraglutide dose and treatment duration in males, and the graph on the right shows the same effect in females. In long-term human clinical trials of Liraglutide, plasma Calcitonin was used as a biomarker for C-cell proliferation, this forced changes in Calcitonin from baseline to weeks 26 or 28. Compared to Placebo, the top three lines, Liraglutide dose dependently increased Calcitonin, Dr. Mahoney will present a more detailed analysis of clinical findings for plasma Calcitonin and thyroid proliferative lesions in her presentation.

Liraglutide had different effects on plasma Calcitonin in mice and rats that are not accounted for by the proposed mode of actions. In rats, Liraglutide had no durable effect to increased plasma Calcitonin or thyroid Calcitonin MRNA, therefore changes in Calcitonin secretion or synthesis probably do not drive hyperplasia and tumor formation in rats, Calcitonin was not a biomarker for drug induced C-cell hyperplasia or tumors in rats. In mice, increased plasma Calcitonin was Liraglutide dose and treatment duration dependant and it was biomarker for focal hyperplasia and tumors. In humans, Liraglutide dosed dependably increased plasma Calcitonin from baseline to weeks 26 or 28 and it is being used as a biomarker for C-cell proliferations. In rats, increased Calcitonin synthesis does not proceed C-cell hyperplasia, but in mice it does. C-cell hyperplasia can be either diffuse or focal and they have different characteristics. In rats, C-cell proliferation occurs along a continuum, normal C-cells proliferating in response to increased blood Calcitonin, blood calcium is diffuse.

Diffuse hyperplasia is a reversible physiological response with cells dispersed throughout the thyroid, it also occurs as rats age. Diffuse hyperplasia cannot be identified by standard tissue staining techniques, such as Hematoxylin Eosin, but it is identified by quantitative analysis of Calcitonin immunoreactive cells. Focal hyperplasia is clusters of C-cells identified by Hemotoxin Eosin stained thyroid tissues. Cells can be enlarged with eosinophilic cytoplasm rounded over nucleus and variable Calcitonin immunoreactivity. The size differentiates adenomas from focal hyperplasia in rodents. Adenomas displaced in the area equivalent to at least five of at least five follicles. The background incidents of focal hyperplasia and adenomas increase with age in rats. Carcinomas show stromal or vascular invasions. A time course for Liraglutide induced C-cell proliferation in male rats was constructed using incidents data from controlling

high dose groups from four, 13 and 26 week toxicity studies, mechanistic studies would sacrifice at four, 30, 43, 56 and 69 weeks, and the 104 week Carcinogenicity study.

This graph shows the time course for the development of Focal C-cell hyperplasia and adenomas in male rats. Gray symbols show the incidence of hyperplasia adenomas in the control group and white symbols show the incidence in the high dose Liraglutide treated groups. Rats less than eight months old have a low background incidence of focal C-cell hyperplasia and Liraglutide had no effect up to 26 weeks, Liraglutide increased the incidence of adenomas after 30 weeks and it increased the incidence of focal hyperplasia after 43 weeks. A time course for Liraglutide induced C-cell proliferation in male and female mice was constructed using incidence data from high dose groups from four and 13 weeks toxicity studies, mechanistic studies, with sacrifice at two and nine weeks, and the 104 week Carcinogenicity Study. This graph shows the incidences of focal C-cell hyperplasia, square symbols, and adenomas, round symbols, from high dose groups for different treatment durations in male mice shown in blue and female mice shown in red.

Consistent with it's rarity in mice, focal hyperplasia or adenomas didn't occur in control groups, so control group data was not included on the graph. Liraglutide caused focal C-cell hyperplasia within 4-9 weeks of treatment and C-cell adenomas occurred in the 104 week study. The time course of Liraglutide induce induced C-cell proliferation in mice and rats are different, but the Liraglutide caused focal hyperplasia, adenomas and Carcinomas in both species. Male rats less than eight months old are insensitive to C-cell proliferative effects of Liraglutide; it accelerated the onset and increased the incidence of adenomas beginning at 30 weeks. Liraglutide increased the

incidence of age related focal C-cell hyperplasia after at least 43 weeks, but without accelerating its onset.

The effects of Liraglutide on C-cells in rats occurred in the absence of any durable effect on plasma Calcitonin. In mice, Liraglutide increased plasma Calcitonin prior to the onset of focal hyperplasia; it increased the incidence of focal C-cell hyperplasia within four to nine weeks. Focal hyperplasia progressed to adenomas. If increased Calcitonin secretion and synthesis drives hyperplasia, then diffuse C-cell hyperplasia was expected to perceive focal hyperplasia and tumors. To show this progression, Nova Nordisk assessed diffuse C-cell hyperplasia in thyroid of mice and rats treated with Liraglutide at doses causing focal hyperplasia but terminated the animals before it developed. Mice were treated for two weeks since rats from the chronic 26 weeks toxicity study did not develop focal hyperplasia, thyroid from controlled and high dose groups were examined.

C-cell mitogenic effects of Liraglutide were also assessed by BrdU labeling and PCNA staining thyroid tissue sections from treated rats. Quantitative analysis of Calcitonin immunoreactive C-cells in thyroid showed high dose Liraglutide did not cause diffuse hyperplasia in male or female mice, treated for two weeks, this table shows there was no significant treatment effect on C-cell density with the ratio of C-cells to follicular cells measures of C-cell hyperplasia in mice treated with 5 milligrams per kilogram Liraglutide. Liraglutide did not cause diffuse C-cell hyperplasia and it was not a C-cell mitogen in rats treated for up to 26 weeks.

The figure on the right shows 1 milligram per kilogram Liraglutide did not increase the ration of C-cells to follicular cells in male and female rats, a measure of diffuse hyperplasia. Liraglutide was not a C-cell mitogen in rats, but these data are not

shown, it did not increase the C-cell PCNA labeling index in high dose treated rats after 26 weeks of treatment and it didn't affect the volume of BrdU labels C-cells and thyroid from rats treated with high dose Liraglutide for four weeks. The Liraglutide did not cause diffuse C-cell hyperplasia in mice or rats, even though they both developed drug induced focal C-cell hyperplasia and tumors. Liraglutide did not cause diffuse or focal hyperplasia in monkeys, and it didn't elevate Calcitonin, but in the absence of hyperplasia in monkeys is not reassuring. Because diffuse hyperplasia didn't occur in treated mice or rats, but they still got C-cell tumors and monkey studies may not adequately assess the risk of focal C-cell hyperplasia and tumors because of the small number of animals treated and the short period of dosing compared to the lifespan. Based on characterization of Liraglutide induced C-cell proliferation, Liraglutide causes focal C-cell hyperplasia but not diffuse hyperplasia in both mice and rats.

Since Liraglutide doesn't cause sustained dose related increases in plasma Calcitonin in rats, and it's not clear that focal hyperplasia is a response to increased Calcitonin secretion and synthesis in the absence of diffuse hyperplasia in mice, these results do not support the proposed mode of action for Liraglutide induced thyroid C-cell tumors in rats and mice.

Mechanistic studies in rats and mice do not adequately support the propose mode of action for the Liraglutide induced thyroid C-cell tumors for four reasons, the mode of action does not account for calcium regulation of GLP-1 receptor agonist induced Calcitonin secretion, either by increasing calcium sensitivity or inhibiting negative feedback. The basis of species differences in thyroid C-cell GLP-1 receptor coupling to Calcitonin secretion was not adequately demonstrated. Increased Calcitonin secretion was not required for Liraglutide induced focal C-cell hyperplasia in rats. So

this key step in the mode of action does not apply to rats. It is unlikely that increased Calcitonin secretion or synthesis drives Liraglutide C-cell focal hyperplasia in tumors in rats. Diffuse hyperplasia and expected physiological response did not perceive focal hyperplasia in rats or mice.

In addition to the lack of adequate support for the mode of action in rodents, even if the mode of action is correct, Liraglutide increased plasma Calcitonin in long-term clinical studies, so it may be operable in humans. Recent results from repeat dose toxicity studies and preliminary results in Carcinogenicity studies show other long acting GLP-1 receptor agonists cause focal C-cell hyperplasia or tumors in mice. So the effects on C-cells appear to be a pharmacologic class effect of long acting GLP-1 agonist. Human relevance of the Liraglutide induced rodent C-cell tumors cannot be dismissed based on the proposed mode of action, there is a potential increased risk of thyroid tumors in humans treated with the Liraglutide. I would just like to acknowledge all those that contributed to the presentation and thank you for your attention.

CLARIFYING QUESTIONS FROM THE

COMMITTEE TO DR. PAROLA

DR. BURMAN: Thank you. We have 15 minutes approximately for your questions for Dr. Parola from the committee. Dr. Tuttle

DR. TUTTLE: I take you back to slide number eight, most of your presentation focused on rats, it's not clear to me that I can use rats to predict what happened in mice, nevertheless using rats to predict what happens in humans. Why did we focus mostly on rats that have a high background rate that increases with age anyway, you know that might be a model for Familial MTC, but that's not the model for the average person in the United States. So why do we focus on rats rather than mice?

DR. PAROLA: So the purpose of the mode of actions studies was to determine human relevance. So for the mode of action to be -- to apply, it should explain the cause of the tumors in both species. So that's why we looked, we focuses on, we looked at actually the cause of tumor formation in both species according to their mechanism of action studies.

DR. TUTTLE: I mean I guess, but we are putting a lot of emphasis on the rat study where there is a high background rate that you could just be stimulating as opposed to the mice, whereas I look down the columns, the rare columns on the mice and the rare columns on the humans looked a lot more representative of the human situation. So your main conclusion that goes to this mechanism or action thing is different than the mechanism of action that we heard from the company, what you evaluated was whether the Calcitonin secretion would cause C-cell hyperplasia and cancer, and I think correctly concluded that's not going to happen, because that's not what most of us think. The mechanism of action I heard from the company was there is something that was causing C-cell hyperplasia that then led to elevated Calcitonin secretion. So at some point, we are going to have to figure out which mechanism of action we are talking about

DR. PAROLA: I evaluated the mode of action that they submitted in the NDA.

DR. BURMAN: Any other questions, Mark.

DR. KONSTAM: Well, I want to ask Mike, I mean I want to comment on your questions because just as a non-endocrinologist, non-thyroid specialist, trying to get my head around this. I guess sort of in my mind frame it differently than what I am hearing, I mean the issue is that there is a very strong signal in rats and when you deal with safety issues, I guess, the honest is to say that the signal doesn't mean anything for

humans. So I mean I guess that's the way I would be trying to get my head around the data, you have this very strong signal in rats and this somewhat lesser signal in mice, I guess, can we prove it's not relevant to humans and I guess, that's where I see that data that was presented, I mean do you want to comment on that?

DR. TUTTLE: Yeah, I mean I think we always get stuck in a tough situation when we have to prove a negative, right? When I have to prove something doesn't do. So when I look at, I look at it more as the rat rather the exception rather than the rule, there seems to be mice data that way, there seems to be monkey data that doesn't seem very convincing. So I think we have to explain a mechanism and it doesn't allow you to say there is no effect. I think what we heard here this morning was sort of an evaluation of mechanism action leaking over into, does this apply to people? Most of what I heard about criticizing the proposed mechanism of action, I agree with, that was a very nice analysis, I guess what I am trying to figure out is whether that mode of action in rats really correlates with people or has any outcome

DR. KONSTAM: So I mean coming back to that, I am still stuck trying to take the Sponsors data and presentation to give me comfort that the rat signal is irrelevant to humans and I guess, what we just heard sort of moved me off of fully accepting some of the things the Sponsor said, I mean I guess that's sort of where I am heading with this.

DR. TUTTLE: Yeah, I mean, I think the rat data raises the question and makes me look really hard at primarily the Calcitonin data in the humans, because I am struck that the human C-cells have GLP receptor or activating that GLP receptor. In terms of thyroid cancer, we know that Calcitonin is a biomarker of C-cell mass and C-cell hyperplasia, it's a precursor to developing focal C-cell hyperplasia in Medullary cancer. So I look at the rat data and I say I really, really need to look at the Calcitonin data in the

people and get a really good handle about whether that's changing or not changing. So I wouldn't say the rat data says no, it's not reasonable at all that there is a mechanism, it raises the question, but then I kind of leave it at that, it doesn't drive me much further that that.

DR. BURMAN: Thank you. Any further questions for Dr. Parola before -

DR. PAROLA: Actually, I'd just like to remind you that, in Liraglutide, as far as drugs that are before us for approval is unique in that it causes these C-cell tumors in both rats and mice in clinically relevant exposures.

DR. BURMAN: I would like to follow up on that, really regarding the possibility of human data that you presented or has been presented. Let me make sure I understand there are some data on Liraglutide or GLP 1 increasing messenger RNA in cell lines, but what about actually in human samples of people who have gotten the medication and then had their thyroids taken out, any other more relevant, clinical human data that you are aware of?

DR. MOSES: With the Chair's permission, there were no evaluations of the six cases in the program for Liraglutide to on Placebo or comparator in regard to Calcitonin staining or Liraglutide, more importantly Liraglutide, binding to their C-cells, which would have been a challenging thing to perform in any case. We certainly do know that the human C-cell is responsive to stimuli such as calcium and we did the calcium stimulation test and there was no change in regard to calcium stimulation in exposure after six months or up to a year exposure with Liraglutide.

So by trying to increase the sensitivity as much as we could both with the calcium simulation test, and I think importantly looking at those individuals who had abnormal baseline Calcitonin levels; we saw no effect of Liraglutide, I think we also have

to remember in this discussion that the rat physiologically is very different in terms of calcium regulation and the role of Calcitonin in that calcium regulation the non human primates of man and as Dr. Tuttle suggested the high background rate is something to consider.

DR. BURMAN: Dr. Parola, any other comments?

DR. PAROLA: No.

DR. BURMAN: Any other questions for Dr. Parola, if not, then let us move on to Dr. Mahoney

FDA PRESENTATION CLINICAL

KAREN MAHONEY, M.D.

Good morning Mr. Chairman, members of the committee ladies and gentlemen, over the next 40 minutes or so, Dr. Derr and I will present information regarding major adverse cardiovascular events from the Liraglutide Development Program. After that, I will be presenting about 15 minutes worth of clinical information relevant to the animal signal of C-cell carcinomas that Dr. Parola just presented. I will begin by describing the Liraglutide product and it's development program. I will then give a brief introduction to the review of major adverse cardiovascular events, which I will often refer to as MACE. Dr. Derr will then introduce some statistical methods considerations after which I will present some results of the MACE analysis. I will then cover some data on human thyroid cancer including Medullary and Papillary thyroid cancers and Calcitonin. The applicant has already presented basic information about Liraglutide and I will therefore be brief, it's a human Glucagon-Like Peptide-1 analog, with a proposed indication to improve glycemic control in patients with Type 2 Diabetes Mellitus.

Native GLP-1 and this analog promote glucose dependent insulin secretion. Linking of insulin secretion to circulating glucose levels reduces the risk of drug-associated hypoglycemia that is seen with drugs such a Sulfonylureas, which promote insulin secretion independently of blood glucose levels. Liraglutide is intended for once daily subcutaneous Injection beginning at an initial dose of 0.6 milligrams with weekly titration up to a maximum proposed dose of 1.8 milligrams. At the time of the mid cycle safety update to the application, there had been 40 completed trials. Five of these were considered the major Phase 3 trials. Importantly for our safety discussion, the development program had not been designed prospectively to permit systematic evaluation of cardiovascular events or thyroid cancer risk. At the t time of that safety update, about 4700 patients have been exposed to Liraglutide for any indication; of these, about 2400 have been exposed for 24 or more weeks, 840 had been exposed for 50 or more weeks.

Due to the trials designs with multiple Liraglutide dose arms, about twice as many patients received Liraglutide as received comparator. This is important when later considering incidents of adverse events. The Phase 2I trials were all randomized and controlled and had a parallel group design. Each had multiple Liraglutide dose arms. There were no placebo controlled monotherapy therapy trials in naïve patients. Those trials, which did include a placebo, were add on trials, where either Liraglutide or a placebo was added to specified background diabetes drugs. Four out of five trials measured the primary endpoint at 26 weeks; one measured it at 52 weeks. Two trials had voluntary open label extensions in which patients stayed on their original randomized treatments. The five major phase three trials included about 2500 Liraglutide exposed patients. This group comprised about 59% of the total Phase 2/3 Liraglutide exposed

population, which was used for the MACE analysis. The designs of the Phase 2I trials are summarized more thoroughly in the briefing document.

One of the trials was a monotherapy trial with Glimepiride as a comparator, Study 1573. Two trials added Liraglutide, Placebo or active oral control to underline Oral D at diabetes monotherapy, trials 1572 and 1436. One trial added Liraglutide or Placebo to underlying at dual oral therapy, Study 1574. One added Liraglutide placebo or Glargine insulin to underlying dual oral therapy, study 1697. The Phase 2I population had slightly more men than women, mean age was 56 years and mean duration of diabetes were 7.7 years. Mean baseline hemoglobin A1c was 8.4 %, mean BMI was 31.3 k/m2. A small percentage of patients were naïve to diabetic drug treatment.

About a third had only received oral monotherapy and about 60% have previously been treated with combination diabetes therapy. Patients with significant baseline cardiovascular disease were excluded, as were patients with significant renal disease. The maximum base line Creatinine allowed was generally 1.3 milligrams per Deciliter for women and 1.5 for men although one trial allowed 1.7.

Only about 3% of patients had a prior history of Myocardial Infarction. 2/3s had a base line history of hypertension. A variety of terms for lipid disorders were present at base line. The applicant reported the baseline incidents of complications of diabetics for three of the Phase 2I trials. At screening, the concomitant illness case report form had a section to record these, but no specific definitions were used and assignment of the baseline term was at the investigators' discretion.

Although 6.1 % were reported to have baseline nephropathy, recall that a baseline Creatinine above about 1.5 was an exclusion criterion. Therefore these were generally not patients with advanced renal disease; 11.4% were recorded as having some type of macroangiopathy, which could include Peripheral Vascular Disease. Baseline retinopathy and neuropathy were reported for 15% and 19% of patients respectively.

I will briefly touch on rescue criteria for inadequate glycemic control in the Phase 2I trials. From eight weeks to 26 or 28 weeks, inadequate control was defined as a fasting plasma glucose of greater than about 239 mg per deciliter depending on trial. For the two open label extension trials after entry into the extension, rescue occurred for fasting plasma glucose of about -- of greater than 220 mg per deciliter. Rescued patients were removed from study. Therefore were not available to experience further adverse events. Rescue withdrawals were more common among patients treated with add on placebo then with Liraglutide or active control.

The review of major cardiovascular events presented several challenges. The development programs had not been designed to be combined into meta-analysis. The trials were of varying durations and had differences in their blinded portions and open label extension periods. Perspectively planned adjudication of cardiovascular events had not occurred and therefore all data necessary for adjudication were not available. High-risk patients had not being specifically included and in fact, there were exclusion criteria for significant cardiovascular conditions, relatively few major adverse cardiovascular events occurred.

Initially the division had requested that applicants with pending applications submit their own analysis of events of myocardial infarctions, stroke or

cardiovascular death. When these came in, we noted significant differences between applicants, in which event terms were chosen, in which analysis methods were used. To facilitate your discussions, the agency made a uniform information request of the applicant to attempt to provide the committee with similar types of information for pending applications. However comparisons across development programs would not be appropriate, because of how different the development programs were.

We wanted an endpoint that would evaluate the incidence of MI or stroke or cardiovascular death. We've described the process for arriving at these endpoints in the briefing document. We chose a broad standardized endpoint in an effort to capture all possible events that could represent MI or stroke. We chose more specific endpoint intended to include only those event terms that seemed more likely to represent actual events of MI or stroke. A list of event terms for both endpoints is in your briefing document. The broad endpoint included cardiovascular deaths and two standard queries from the medical dictionary for regulatory activities. Broad myocardial infarction and broad central nervous system hemorrhages and Cerebral Vascular Accidents.

These queries are intended as broad nets to capture all events that might represent a category. The resulted broad composite endpoint was perhaps not very specific for MI or stroke, for example the term increased creating phosphokinase accounted for 46% of all the events that actually occurred, but none of the patients who had an event of increased CPK also had an MI or stroke. The broad MACE endpoints also did not include a couple of potentially relevant events, which did occur. The more specific endpoint is referred to as the FDA custom endpoint it's not a standard FDA endpoint and should not be presumed to be the agency's choice for future evaluations of cardiovascular events. It is a subset of events from the broad MACE endpoint and

includes terms, which were considered more likely to represent actual events of MI or stroke.

The process by which the term was chosen is included in your briefing document, we fully acknowledge that this process has limitations others might have chosen a somewhat different set of terms. The analysis included two seriousness categories; all treatment emergent events are only those, which met a commonly used regulatory definition for serious events. Comparisons were made of Liraglutide to combine placebo in active control with subgroup analysis versus active comparator and versus placebo. Two-time period populations were used. The first called population A included the randomize control portions of all Phase 2, III trials out to measurement of the primary endpoint. Population A is probably more interpretable than population B, which added the control but unblinded voluntary extensions that I mentioned earlier. Dr. Derr will now present an overview of statistical methods considerations.

FDA PRESENTATION CLINICAL

JANICE DERR, M.D.

We analyze the incidence ratio, which is the ratio of the percentage of patients with MACE events in the Liraglutide arm divided by the percentage of patients with MACE events in the comparator arm. When events are relatively in frequent as is the case with Liraglutide, the incidence ratio was for practical purposes, the same as the odds ratio, which was discussed yesterday with Saxagliptin. We also analyzed two other forms of the endpoint but we are focusing today on the incidence ratio, we analyzed the incidence ratio adjusted for patient years of exposure.

We found that the results for the adjusted ratio were similar to the unadjusted ratio and we analyzed the incidence difference. We focus today on the

incidence ratio because the goalposts describe 1.3 and 1.8 described in the cardiovascular guidance were developed for ratios, we use several different methods to calculate the 95% confidence bound of the incidence ratio, and all of the estimates we use were stratified by study. We believe that a stratified analysis is the best way to provide a meaningful estimate of the upper 95% bound. However, in a stratified analysis, the estimate is challenging because of the overall infrequency of the MACE events. We found that the Liraglutide versus total comparison was not very sensitive to method. The sub group Liraglutide versus placebo comparison was sensitive to method. The reason we use methods that were stratified by study was that we believe this approach gives a meaningful estimate in the situation where studies have different allocation ratios between the Liraglutide group and the comparator group.

These differences are due to differences in the designs of the 15 studies used in the MACE analysis, studies differed in the number of Liraglutide dose arms and they had, either a placebo control group, an active comparator group or both a placebo and an active comparator group. For each comparison, we included only those studies that have the comparator arm we were evaluating. For example, the Liraglutide versus placebo comparison included the 12 studies that had a placebo arm. The allocation ratio of Liraglutide to placebo in these 12 studies ranged from six to one to two to one.

The challenge to using a stratified estimation method in this situation is the overall in frequency of the MACE events. Some studies had zero events in either the Liraglutide group or the comparator group or both groups. In this situation, the estimation methods can be sensitive. The upper 95% confidence bound may vary depending on the method used to estimate it, because we are especially interested in comparing the upper 95% confidence bound to the goalpost of 1.3 and 1.8, we wanted to

make sure that this estimate is reasonable and not very sensitive to method. This graph demonstrates the sensitivity to method that we have found in the subgroup comparison Liraglutide versus placebo, each set of three confidence intervals represents three different methods applied to one incidence ratio. The top three intervals are from the custom MACE endpoint in population A. The confidence interval shown in black which is the top one of each triple, comes from a stratified Mantel-Haenszel method, the intervals shown in red, which are the middle ones in each triple come from a stratified exact method and the interval shown in blue, which is the bottom one in each triple, come from a fixed effects meta analysis with a continuity correction of 0.5 added to studies that had zero MACE events in one or both groups.

You can see that the upper 95% confidence bound ranges from about 1.3 to beyond 1.8 across the set of 12 estimates. This is what we mean by sensitivity. The three estimations methods that we use each had advantages and disadvantages in the stratified analyses of events that are in- frequent. For this reason, we did not identify any one event as preferable to the others; instead we use the methods to evaluate the sensitivity of the results to method. The stratified Cochran-Mantel-Haenszel method is a well-established method for estimating an incidence or odds ratio. A disadvantage to this method is that studies with zero events in both the Liraglutide and the comparator groups are omitted from the estimate. In addition, when events are infrequent the assumptions used in the asymptotic estimation may not be met. The stratified exact method was also omits studies with zero events in both groups.

The assumptions used in the estimation method are appropriate even when events are in frequent. However the confidence interval would tend to be conservative in this situation. The fixed effects meta-analysis that we use does include all the studies,

because a continuity correction was added to each category and studies with zero events. However in this situation when events are infrequent, the continuity correction itself can be very influential. This Forest plot depicts the results for each study in the subgroup Liraglutide versus Placebo comparison. Each study has a confidence interval shown by the horizontal line. The results for Liraglutide and Placebo are given over to the side. The endpoint is custom MACE and population A.

The estimation method is the fixed effects meta-analysis that I have discussed in the previous slide. The size of the midpoint symbol is proportionate to the precession of the estimate. So you can see some estimates are more precise and some you can't even see the symbol, they are not very precise at all. You can see that seven other studies, which are the top six studies and the one on the bottom, have zero events in both groups in very broad confidence intervals. Three other studies have zeros in the Placebo group so those are, you know, in this situation adding a continuity correction will be influential.

This figure shows the comparison of the sub group Liraglutide versus active comparator and it was less sensitive to method. Most of the upper bounds were in the range 1.3 to 1.8. The comparison of Liraglutide to total comparator was also less sensitive to method. All of the upper 95% confidence bounds were less than 1.8. So Dr. Mahoney will now continue her presentation of the MACE analyses.

DR. MAHONEY: I will now present the results of the MACE analyses. Dr. Derr has alluded to some of these results but I will specify them. I am presenting them with three important values in mind that relate to the cardiovascular events guidance for diabetes products that Dr. Joffe described. First what is the point estimate of the risk for Liraglutide versus comparator? Second I will present how the upper

bounds of the 95% confidence intervals fall with respect to that boundary of 1.8, which was a boundary above which the guidance states that further study of cardiovascular events would be needed prior to approval.

I will then consider where the upper bounds of 95% confidence intervals fall with respect to 1.3 in the guidance products that had values greater than 1.3 and less than 1.8 could be considered for approval, but we require adequate post marketing study to provide reassurance of cardiovascular safety. I will begin with the comparisons of Liraglutide versus total comparator, for these estimates, our point estimates were less than one favoring Liraglutide and all upper bounds were less than 1.8. However, the upper bound was usually greater than 1.3. These results were not very sensitive to analyses method; results were similar for different endpoints time period, populations, events seriousness groupings and statistical analysis methods.

This table presents the analyses performed by the applicant using a stratified asymptotic Cochran-Mantel-Haenszel method. Don't worry about all these "X"s they just represent the analysis scenario that you are dealing with. What's important are the two right hand columns, this column illustrates how the point estimates are all less than one for Liraglutide versus comparator regardless of endpoint event seriousness grouping or time period population. Looking at the upper bounds of the 95% confidence interval you will note that they are all less than 1.8 but almost all greater than 1.3. This table presents Dr. Derr's analyses for Liraglutide versus total comparator by two methods, using all treatment emerging adverse events. The four rows that are shaded in yellow are for analyses by an exact method.

Again look at the two right columns, again point estimates less than one and upper bounds between 1.3 and 1.8. Below the shaded area in the bottom four rows

are Dr. Derr's analyses using asymptotic fixed effects Mantel-Haenszel method with a continuity correction of plus 0.5 for arms with no events. Again point estimates are less than one. Recall that analyses by this method will result in a less. Excuse me; in this case, upper bounds are near 1.3.

Recall that analyses by this method will result in less conservative estimates then the others using the exact method. This slide illustrates those results graphically; the graph includes the FDAs analysis and the corresponding analysis using, Nova's method. This vertical line represents a point estimate of 1.0, this 1.3 and this 1.8. Point estimates to the left of the 1.0 favor Liraglutide. The 1.3 line and the 1.8 line are useful in illustrating how the upper bounds of the 95% confidence intervals fall relative to the boundaries mentioned in the cardiovascular evaluation guidance. For each horizontal bar, the middle symbol represents the point estimate and you can see that they are all less than one favoring Liraglutide.

When examining the upper bound of the 95% confidence interval, you can see that all values fall to the left at this 1.8 line that are near or to the right of this 1.3 line. Looking at these upper bounds as a group, they don't vary a great deal in value supporting that these results are not very sensitive to analysis method. Results for a subgroup analysis of the Liraglutide versus only active comparator were qualitatively similar to those for Liraglutide versus total comparator, point estimates were again less than favoring Liraglutide. Now upper bounds were usually but not always less than 1.8, upper bounds were again usually greater than 1.3, these estimates were somewhat sensitive to analyses method, but had fairly similar results when one analyzed using the various scenarios. Again the Nova analyses using their asymptotic CMH method point estimates, less than one. Upper bounds here are less than 1.8 and generally above 1.3.

Dr. Derr's exact method analysis results are in the four-shaded yellow rows, point estimates less than one, upper bounds here was one greater than 1.8 and all greater than 1.3.

Results for Dr. Derr's meta-analysis method with continuity correction are in the bottom for unshaded rows. Point estimates less than one. Upper balance is less than 1.8 covering near 1.3. Again this method because of its continuity correction for arms with zero events, results in less conservative values and those obtained with the exact method. You may recall the previous plot for Liraglutide versus total comparator and you can see that for active comparator looks qualitatively similar. Point estimates are less than one. Most of upper bounds are less than 1.8 except for one up here. Most are at or above 1.3, there is only a little bit more sensitivity to method. The results for subgroup analysis of Liraglutide versus Placebo are somewhat different; here the point estimates were often greater than one, not favoring Liraglutide. The upper bounds of the 95% confidence interval were often greater than 1.8 and usually greater than 1.3, here there was sensitivity to analysis method, results varied by endpoint, population, seriousness grouping and analysis method.

Recall that the guidance does not require applicants to meet specified 95 % confidence interval boundary limits for subgroup analysis. Here in Nova's estimates by their asymptotic CMH method, here you note that several of the point estimates are greater than one, this time not favoring Liraglutide. Here you note that all of the upper bounds of the 95% confidence intervals are greater than 1.8, sometimes considerably greater than 1.8. For Dr. Derr's exact analyses note that four top shaded rows, again point estimates sometimes greater than one. Upper bounds are always greater than 1.8. For Dr. Derr's meta-analysis method with continuity correction in the bottom four un-

shaded rows, the addition of the continuity correction was influential, here point estimates are less than one, and upper bounds are less than 1.8, but generally greater than 1.3.

Now recall those other plots we looked at, this one for Liraglutide versus Placebo looks different. Here you can see that point estimates are not always less than one and sometimes don't favor Liraglutide, you can also see that the upper bound is usually greater than 1.8. You can also see that there is a lot more variability in that upper balance value reflecting the sensitivity to method that we mentioned. Why were some point estimates greater than one for subgroups analysis of Liraglutide versus Placebo, one might wonder at first if it was because the Placebo treated patients were simply at lower risk population and would be expected to be at lower cardiovascular risk than Liraglutide treated patients. However recall that these analyses were stratified by trial, only those trails, which used to Placebo control were included. Also the Placebo trails weren't mono therapy trials in naïve patients, they were add on trials.

We examined cardiovascular risk factors in the Placebo control trials and they were not gross differences by treatment group. Therefore, difference in risk probably does not explain it. You may recall that more placebo treated patients were withdrawn from study for an adequate glycemic control and therefore a few of them may have been available to have events. Nova did some analyses that took patient-year exposure into account, which had somewhat lower point estimates for Liraglutide versus Placebo. These analyses results are in the FDA briefing document.

The observed sensitivity to method is probably explained in large part by low event rates, looking at all events that contributed to these analyses the analyses with the largest number of included Placebo events which was the broad SMQ all treatment-

emergent events population B scenario, there were only third team Placebo treated patients with events. For the more specific analyses of the FDA custom endpoint, serious events in population A, there were only two patients. Low event rates also contributed although to a lesser degree to some sensitivity to method seen for analyses of Liraglutide versus active comparator.

Low event rates present a major challenge to assessing the risk of truly clinically significant cardiovascular events for Liraglutide. This slide has a lot on it, but I'll walk you through it, it give some examples of raw event numbers and of the effect of changes and analyses scenario on event rates. There were many possible analyses scenarios, but I've only included a few examples. The first column tells you which endpoint we are discussing. The second column tells you which combination of analyses factors were included as an example. The next column describes what has changed about the scenario from one row down to the next. The next three columns give overall treatment groups with a number and percentage of patients who had an event for the given scenario. The right hand column gives the major reason for the decrease in number of events from the rows above.

The top three rows are three scenarios using the broad SMQ endpoint. The top row includes a scenario with the most events of any scenario, the broad endpoint, all serious and non-serious MACE events and the population that included both the main trial and the extension data, population B. Now don't compare the percentages, they are just row numbers and they don't reflect stratification by trial, because of Liraglutide column includes all Liraglutide treated patients. Let's concentrate on this middle shaded column for Liraglutide treated patients first. Here you can see the generally low event rates. For example 69 are 1.6% of all the Liraglutide treated patients had any event.

Now go down and switch from population B to population A, which didn't include unblinded extension data, recall that we consider population A to be more interpretable than population B, however less observation time fewer events, 69 to 51. Now go down to the next cell, where you changed only serious events and you get a big drop from 51 to 16, why? That's mostly because that half the events and broad SMQ were increased CPK, and they were almost all non serious. Now let's look at the bottom three rows, where we are dealing with scenarios with the FDA custom endpoint.

Look here, 21 events for custom, 69 for broad, with all other things being equal in the scenario. Why is this? Mostly because the FDA custom endpoint didn't include CPK events, as well as some other mostly non-serious event terms. For FDA custom taking out extension data drops you from 21 to 13 events. Now here taking out non-serious events doesn't change the number much going from 13 to 11. The FDA custom endpoint turns out to be pretty specific for serious events although we were blinded to that when we chose the terms to include.

One final point, look at the Placebo column. You see here that the event numbers in the Placebo group were indeed low especially as you go down the column. The main overall point for the slide is that event rates were low, especially when you try to include the most relevant events and the most interpretable time periods. What were those events and why were there are such different numbers for the broad SMQ and FDA custom endpoints. This table includes the most common even terms for events, which accidentally occurred.

The first column list the events, the next three columns give the number and percentage of patients who had these events for each treatment group. With this being all patients Liraglutide plus comparator this being Liraglutide and this being

comparator alone. The two far right columns tell you whether the term was included in the broad SMQ or FDA custom endpoint. About half of all the events, which occurred were events of increased CPK, this event was included in the broad SMQ endpoint, but not Interviewer: FDA custom endpoint. It accounts for much of the difference between the number of events for the two endpoints. CPK was routinely measured, the vast majority of these events were non serious and these patients did not appear to have other events of MI or stroke.

They are split evenly between Liraglutide and comparator. Fifteen patients had an event termed myocardial infarction and 12 had acute-myocardial infarction. These were split fairly evenly between the Liraglutide and comparator. Carotid Artery Stenosis and Transient Ischemic Attack occurred in a total of seven and six patients respectively. These terms were also not in that FDA custom endpoint. Cerebral Infarction and Cerebral Vascular Accident occurred in four patients each. Again split fairly evenly between the Liraglutide and comparator. Both these terms were included in both endpoints.

Regarding total mortality, there were only four post-randomization tests for Liraglutide treated patients and three for a comparator. The overall death rate was low and there was not a pattern of causation. To summarize observations regarding MACE, the development program was not prospectively designed to permit systematic evaluation of cardiovascular events. Events did not undergo preplanned adjudication and adequate data were not available for post-hoc adjudication. Few high-risk patients were included and few major cardiovascular events occurred, which presents a major challenge to the assessment of cardiovascular risk.

Results for Liraglutide versus total comparator and the subgroup analysis of Liraglutide versus active comparator were qualitatively similar. With most point estimate less than one and most upper bounds of 95% confidence intervals between 1.3 and 1.8. For the subgroup analysis of Liraglutide versus Placebo point estimates were often grater than one, not favoring Liraglutide and upper bounds were often greater than 1.8. The results were sensitive to analysis method. Low event rates contributed to this observation, recall that the guidance for evaluation of cardiovascular risk does not specify that boundary limits must be met for subgroup analysis. We did examine results by dose, and there was no apparent relationship between Liraglutide dose and risk of MACE. The rate of total mortality was low and there was no cause specific pattern.

Okay, so switching gears to thyroid cancer and Calcitonin. You know, I'm an Endocrinologist and I think there are two kinds of people in the world, Endocrinologists and non- Endocrinologists. You know, you might not be able to tell it by looking at them, but if you had been a fly on the wall, when they open the briefing document, you would have been able to tell, because the Endocrinologist opens it up and they all go, an animal signal a possible Medullary Thyroid Cancer, cool. Yeah, you know you did. So any way, we now get to talk about Medullary Thyroid Cancer and Papillary Thyroid Cancer and Calcitonin, which is excellent. I will begin by reiterating a few key points from the animal data. In carcinogenicity studies, Liraglutide was associated with development of C-cell tumors in two species in both genders at clinically relevant exposures. A similar signal is being noted for some other long acting GLP-1 analogs in development. Mechanistic studies may not have definitively demonstrated that this risk is relevant only to rodents and not to humans. No drug with the C-cell finding is known to have been approved, historically it appears and it is very rare for a drug that has caused

tumors of any cell type in two species at clinically relevant doses to have been approved regardless of mechanism. A bit of background about Medullary Thyroid Carcinoma it's a relatively rare cancer, which arises from the C-cells of the thyroid gland.

There are sporadic and familial forums. These cancers often had mutations of the rearranged during Transfection or RET proto-oncogene. These mutations are useful in screening kindreds or probands with Medullary Thyroid Cancer. C-cells normally produce Calcitonin and Medullary thyroid cancer cells often produce it in excess. Therefore Calcitonin can be a clinical marker. The tumor is relatively indolent although not always, because of this indolence one might not expect to see cases of Medullary Thyroid Cancer over the duration of the typical drug development program, even if the drug was causing it.

Early complete surgical excision is probably the only curative option. When complete resection is not possible palliative treatments are often attempted. These patients usually have Medullary Thyroid Cancer as their cause of death rather than another cause. Local neck invasion with Asphyxia or other local invasion is often the cause of death in non-resectable cases. Today there has not been a clearly described association between a particular drug in non-increase risk of Medullary Thyroid Cancer. In the Liraglutide development program there were no cases of Medullary Thyroid Carcinoma among the Liraglutide patients, and one among comparator treated patients. There were two cases of neoplastic C-cell hyperplasia, which is sometimes called medullary carcinoma in situ.

One in a Liraglutide treated patient and one in a comparator treated patient. C-cell hyperplasia will be discussed later, but it is often divided into diffuse and neoplastic forums. There is controversy in the medical literature regarding the validity

and clinical significance of this distinction. Neoplastic C-cell hyperplasia may be more likely than diffuse C-cell hyperplasia to progress to Medullary Thyroid Cancer. The comparator treated patients who had Medullary Thyroid Cancer were reported by the applicant after the briefing document deadline. Therefore there is no narrative for this patient in your briefing document.

This 61 old man had a baseline Calcitonin value of over a thousand nanograms per liter, which is markedly elevated. During the study, an ultra sound showed replacement of the right low by a four-centimeter nodule, fine needle aspiration was inconclusive. After study completion, total thyroidectomy reveled Medullary Thyroid Cancer with typical structural features and multiple positive stains. There was Extracapsular Spread and Endovascular and Endolymphatic propagation of the tumor. The Liraglutide treated patient who had Neoplastic C-cell hyperplasia had a mildly elevated baseline Calcitonin of 22.3 nanograms per liter. He received Liraglutide 1.8 milligrams for 26 days. During the study, he underwent Thyroid Ultrasound, which reveled a Hypoechoic Lesion in the left upper pole. He underwent Thyroidectomy.

The pathology report and the subsequent confirmatory pathology consultative report both state that the findings were consistent with Bilateral Neoplastic C-cell hyperplasia, which is sometimes also referred to as Medullary Carcinoma in situ. There were numerous parafollicular aggregations of atypical C-cells. One-millimeter focus of papillary thyroid carcinoma was also noted. The comparator treated patient, who was found had Medullary Carcinoma in situ had a baseline goiter in normal Calcitonin. Three months in the study, he had a mild elevation in serum Calcitonin. Near the end of study, he reportedly had an abnormal Pentagastrin Stimulation Test; he underwent Thyroidectomy. Pathology reveled Multinodular Goiter and Bilateral

Neoplastic C-cell hyperplasia, immunohistic chemical staining for Calcitonin was positive, with parafollicular aggregates of normal C-cells.

Switching for a moment from Medullary Thyroid Cancer to Papillary Thyroid Cancer, in the development program, there were six cases of Papillary Thyroid Cancer identified for Liraglutide treated patients and one case identified for a comparator treated patient. For all but one of these cases there is a narrative in your briefing document. One case in a Liraglutide treated patient was reported after the briefing document deadline and is presented on these slides, but is not your briefing document. You may recall that overall there are about twice as many Liraglutide treated patients as comparator treated patients in the development program. So this comes out to a ratio about three to one. The following slide shows this and the next present some information about these cases. The ages of the affected patients are fairly typical for Papillary Thyroid Cancer and there was gender imbalance.

Four out of the six cases for Liraglutide treated patients occurred among patients treated with the highest dose, the 1.8 milligrams per day. All were exposed for less than one year. More information about those same seven cases of Papillary Thyroid Cancer, the comparator treated patient and all but one of the Liraglutide treated patients had elevated Calcitonin preoperatively. The patient who did not have an elevated pre-op Calcitonin had a baseline goiter with a dominant nodule. All of the patients went to surgery because of Calcitonin or Thyroid ultrasound findings that were done as part of clinical trial monitoring. Most of the tumors were small in the range of one to two millimeters. This raises the question of whether these were incidental Papillary Microcarcinoma.

Three of the six Liraglutide treated patients who had Papillary Thyroid Cancer also had C-cell hyperplasia on pathology. None were described to have lymph node involvement or metastasis. The comparator treated patient who had Papillary Thyroid Cancer did not have C-cell hyperplasia described on pathology. Specifically regarding C-cell hyperplasia, there were a total of three cases among Liraglutide treated patients excluding the previously described case of Medullary Carcinoma in situ. Two of these three patients also had a small Papillary Thyroid Cancer and were presented in the previous slides. There were no comparator treated patients of C-cell hyperplasia excluding the previously described cases of Medullary Thyroid Carcinoma and Medullary Carcinoma in situ.

All cases were diagnosed through preplanned clinical trial monitoring or Calcitonin and had relatively mild pre-operative Calcitonin elevations. This slide presents some information about the C-cell hyperplasia cases and includes the cases of Medullary Carcinoma in situ. All but one were males, exposure ranged from 28 to 484 days. Pre-operative static Calcitonin elevations were mild, the upper limit of normal for men for the assay used by the applicant was 8.4 nanograms per liter. This column presents static base line Calcitonin values, this line presents pre-op static Calcitonin values were available, and this line presents the peak stimulated Calcitonin on a calcium stimulation test if it was available. The applicant defined a value of greater than 90 is abnormal for women and a value of greater than 130 as abnormal for men on the calcium stimulation value.

The cases, which were not described as Medullary Carcinoma in situ were described as Diffuse C-cell hyperplasia. The applicant monitored Calcitonin in some of its clinical trials, Calcitonin is synthesized in several mammalian tissues, but thyroid C-

cells are the primary side of synthesis. Normal human circulating levels are very low, it has an inhibitory effect on Osteoclast mediated bone resorption. There may be multiple stimuli for release, relative to this discussion Calcitonin has historically served as a clinical marker for Medullary Thyroid Carcinoma. However there is a great deal of controversy in the medical literature about the usefulness of Calcitonin for screening for Medullary Thyroid Cancer. With several studies suggesting a low positive predictive value for Mild Calcitonin Elevations, also the circumstance we are now dealing with is apparently unique. No one has experienced in using Calcitonin to screen for a possible drug induced Medullary Thyroid Cancer. It's mostly been used to screen family members of patients with non-medullary thyroid cancer. Static levels of Calcitonin were measured at base line and during the five long-term Phase 2I trials and in some shorter trials.

Dynamic calcium stimulation testing was done on a sub population from two of the long-term trials. Neither of these testing scenarios demonstrated a Liraglutide associated risk of marked elevation in Calcitonin. However although its effects were not marked, Liraglutide may have had some effects on Calcitonin levels. One of the ways Calcitonin was examined was to look at shifts from one category of Calcitonin value to one another. For example, from below the lower limit of quantitation to within the range of quantitation or from the normal range to above the normal range. For both genders, the majority of patients began with values that were bellow the lower limit of quantitation. This slide shows the percentage of women, who shifted from below the lower limit of quantitation to within the range of quantitation, from baseline to 26 or 28 weeks.

As you can see, there was a dose depended trend from more Liraglutide treated than comparator treated women, to shift from below the lower limit of

quantitation to within the range of quantitation. The percentage of women who exhibited the shift was numerically higher for each of the Liraglutide dose groups than for either active or a Placebo comparator. Men began with somewhat higher baseline levels and this trend was not seen for them. This table sums the total percentage of patients who had any upward shift in Calcitonin levels. For example, it adds up those who shifted from below the lower limit of quantitation to within the range of quantitation and those who shifted from detectable levels to above the upper limit or normal. Here the treatment group with the highest numerical percentage of upward shifters for both genders, was the highest Liraglutide dose group, 1.8 milligrams, here in the bottom row.

The 1.8 milligram dose group had a numerically higher percentage of upward shifters than either of the other Liraglutide dose groups and a higher percentage than either Placebo or active comparator. However dose dependency for Liraglutide was not demonstrated. The applicant also analyzed mean Calcitonin values in the long-term trials, values at 12 and 26 weeks are presented on the slide, the main point I want to make from this slide is that the lower limit of quantitation for the assay was 0.7 nanograms per liter. The mean values at these time points do not fall much above this. Most patients have baseline fell below the lower limit of quantitation therefore analysis may have been influenced by how the applicants model handle values that were below the lower limit of quantitation.

This slide shows the relative percent differences in main Calcitonin values at week 12 for Liraglutide versus comparator. The agency considers these analyses to be exploratory. However, for all comparisons of Liraglutide to placebo and for Liraglutide comparisons to active comparator, the relative percent difference was statistically significant using the applicant's model. At 26 weeks, the relative percent differences for

Liraglutide versus placebo remained statistically significant but those for Liraglutide versus active comparator did not.

This slide illustrates those mean percent differences at 26 weeks graphically. The horizontal line across the bottom represents percentages. Values to the right of zero indicate that the agent of interest was a certain percentage higher than the comparator. Here you can see that for Liraglutide versus placebo, the differences were statistically significant using the applicant's model and there was a dose dependent trend. For Liraglutide versus active comparator, the relative percent differences were not statistically significant although the dose dependent trend may still be present. This pattern of dose dependence was not demonstrated at some other time points, however.

To summarize observations regarding thyroid cancer and Calcitonin, Liraglutide was associated with C-cell tumors in mice and rats in both genders at clinically relevant exposures. A similar signal is being noted for some other long acting GLP-1 analogs in development. Mechanist studies may not have definitely demonstrated that this risk is specific to rodents. No drug with a similar set of C-cell tumor findings is known to have been approved. It is very rare for a multi species carcinogen, for any cancer cell type 2 have been approved regardless of mechanism.

There was not a clear case of medullary thyroid cancer for any Liraglutide treated patients but one might not expect to see this relatively indolent tumor over the duration of a drug development program. Neoplastic C-cell hyperplasia also sometimes known as medullary carcinoma in situ occurred in one Liraglutide treated and one comparator treated patients. There were six cases of papillary thyroid cancer for Liraglutide treated patients and one for comparator treated. Recall that there are about twice as many Liraglutide treated patients overall so this is about a three to one ratio.

Most of the papillary thyroid cancers were small, was surgery prompted by per protocol Calcitonin screening. Three of the six patients who had papillary thyroid cancer also had C-cell hyperplasia with two diffused and one neoplastic case. There was one additional case of diffused C-cell hyperplasia for a Liraglutide treated patient.

The use of Calcitonin to screen for medullary thyroid cancer is controversial and no one has experience in using Calcitonin to screen for drug induced medullary thyroid cancer. Analyses of Calcitonin values did not demonstrate a Liraglutide associated risk of marked elevation in Calcitonin in humans. In long-term trials, there was a dose dependent trend for women to shift from below the Lower Limit of Quantitation to within the range of quantitation with higher numerical values for all Liraglutide dose groups than for comparator. Overall, upward shifts of Calcitonin occurred numerically most commonly among patients treated with the highest dose of Liraglutide 1.8 mgs. However, dose dependence was not demonstrated.

Most patients started with low Calcitonin values and mean changes were small. The clinical significance of small changes in Calcitonin in this setting is uncertain. Analyses should be considered exploratory, using the applicants model at week 12, mean Calcitonin levels were statistically significantly higher for all doses of Liraglutide and for placebo or active comparator. At week 26, values remained statistically significantly higher for Liraglutide versus placebo but not for active control. At 26 weeks, there was a dose dependent trend for both Liraglutide versus placebo and Liraglutide versus active control. Dose dependency was not demonstrated at some other time points.

A couple of final considerations; thyroid nodules are common in the general population. A thyroid nodule associated with an increased Calcitonin level might be more likely to go to surgery. Enhanced monitoring with Calcitonin or ultrasound

might result in an increased rate of thyroidectomy. Whether or not Liraglutide induces thyroid cancer, it might induce thyroidectomies. This needs to be considered because thyroidectomy has known anesthetic and surgical risks such as recurrent laryngeal nerve injury and vocal cord paralysis and hyperparathyroidism.

Many colleagues have contributed to the review of Liraglutide and I would like to acknowledge these individuals in particular. Thank you.

CLARIFYING QUESTIONS FROM THE

COMMITTEE TO DRS. MAHONEY AND DERR

DR. BURMAN: Thank you, Dr. Mahoney. I would like to open the discussion for the next 15 minutes until noon for our questions specifically for Dr. Derr, Dr. Mahoney. If I might, I would like to ask just for point of clarification to make sure I understand looking at slide 64 on page 32. It gives the increased percentage of rise in Calcitonin. If I understand that right, that's approximately a 10% rise in Calcitonin for values that are starting approximately one or two or three picogram per mill. So it's going up well within the normal range and I would like to know in addition what percentage of people went outside the normal range during this study.

DR. MAHONEY: That's correct. These are small changes from a low mean baseline value and it might actually be better for the applicant to tell you the total percentages that we have on the slide up here.

DR. MOSES: So we have, of course, looked at the shifts, if you will, of Calcitonin from the normal range. Dr. Zdravkovic presented that shift in his core presentation in terms of those who changed. Can we have the core slide up first please. Thank you, we will pull that up in just a moment. Is the slide on, please? So these are data that you have seen in the core presentation. It actually looked at individuals who

had shifted to greater than the upper normal range at various weeks this is 20 - the week 20-28 all the way up to week 78 or 18 months and there is no imbalance in terms of the subjects. I mean there is some switch across different groups but no pattern at all in terms of shifting to greater than the upper level range.

DR. BURMAN: Thank you, about 2%, let me open it up for --

DR. MAHONEY: I just have one comment to make of course which is, you probably noticed in the briefing document that when you look at the Calcitonin daily for the five phase 2I trials that beyond 26 weeks you begin to have quite a few people with missing data and you may also recall that four out of those five trials participation beyond 26 weeks was voluntary and unblinded. So, you would have to take that into consideration when you are thinking about shifts. Did the patients choose to continue and why did they not if they didn't and did they actually have data to evaluate?

DR. BURMAN: Thank you. Dr. Tuttle.

DR. TUTTLE: To continue along that same line, on your slide number 62, just so I make sure, I understand, so these are the real numbers, the mean values like 0.6, 0.7, 0.7?

DR. MAHONEY: Well, they had to deal with the - the applicant can tell you for sure, but they had to deal with values below 0.7 somehow and I believe that they imputed values below 0.7 and 0.35.

DR. TUTTLE: Got it.

DR. MAHONEY: They can tell you for sure what they did.

DR. TUTTLE: I mean to put this into a clinical perspective, the clinical assays that most of us use, read either less than five or less than two. So a large part of

these numbers on here in my clinic would be undetectable. They are using a much higher assay than what we typically use in clinical practice, if I'm reading this right.

DR. MOSES: You are reading that correctly.

DR. TUTTLE: We can comment specifically about the assay in the way that they were handled if you want to do that at this time.

DR. BURMAN: I think the point is made, thank you. Dr. Konstam?

DR. KONSTAM: Thanks. I just want to ask you about the comment that you made with regard to the MACE drug versus total comparator analysis that the findings were not sensitive to the analytic method and I guess I just want to challenge you on that a little bit and I guess it's in the eye of the beholder but we could look at, I guess your slide 33. I mean, one of the things I think we should be avoiding is sort of holding the 1.8 number up to some holiness, right, and I guess if I look at the top analysis which I think is a good one to look at because it's custom MACE population A , the most specific, I guess of all the analyses. I see an upper boundary with one analysis around 1.3 and the other analysis in terms of the upper boundary around 1.8 with the exact method. I don't know.

DR. MAHONEY: I just want to get you to the slide. I think you are actually referring to; this is total comparator.

DR. KONSTAM: Well any one. I don’t think it makes much difference. If you see what I mean, I mean you know we are really going to focus on the upper boundaries here and given that you know, there are a lot of issues with this data set in terms of their non pre-specification and non adjudication and all that stuff, so it would be nice to have some comfort and I guess the amount of comfort I get from an upper boundary of 1.3, upper boundary that just hovers around 1.8 seems to be a big difference

to me based on the analytic method. So, I don't know that you want to stick to your statement or retract it or what?

DR. MAHONEY: Well, one thing I want to talk about just for a minute is why we even looked at sub groups of active in placebo and we had requested that analyses be done where it was broken down by comparator and but when we were taking an overall look at all of the results, when you looked for point estimates that were greater than one and upper bounds that were greater than 1.8, they were all in the comparisons to placebo. That's why we ended up looking at this sub group is particular but I agree with you and part of it is that, the custom endpoint was more specific and cut out a lot more events. So when you have fewer events you are going to have different boundaries perhaps. I will get into statistical problems really quick, so I just probably defer to Dr. Derr.

DR. BURMAN: Thank you. We have a couple of minutes and we have two questions, one by Dr. Veltri and Dr. Proschan. Dr. Veltri?

DR. VELTRI: Thanks. Well, as a non-endocrinologist I will ask you an endocrinology question. I'm a little struck by the slide you showed where you looked at active comparator versus placebo, which showed, it seemed as though there was a defect there on that Calcitonin and then on the Sponsors slide, it looked like the greatest proportion of patients who had - a proportion of patients greater than the upper limit to normal seemed to also be from the active comparator side, indeed there seemed to be a time dependence. So my question really is, what is your make of all that? It seems to be a fairly non specific finding and what is your?

DR. MAHONEY: What do I make of the fact that there also appears to be, by the applicant's model, higher and mean Calcitonin values for active comparator versus placebo that?

DR. VELTRI: Your own analysis where you showed that change in Calcitonin levels, the active comparator versus placebo, I think on slide 64 or whatever and then the subsequent slide from the Sponsor, looked at those greater, yeah, the bottom analyses. Then the Sponsor's slide looking at, I think it was one, two, three years or something like that, that was above upper limit and one above the upper limit and normal. The greatest proportion of patients was indeed you know, on the active comparator versus placebo. So, is this relevant?

DR. MAHONEY: Well, it could be. I do talk about that in the briefing document a little bit. There are multiple potential stimuli for a Calcitonin release and what I don't know is if other anti diabetes drugs could also have some effect on Calcitonin, when you look at the comparisons of Liraglutide to active control for the most part Liraglutide had higher percent differences than active control and definitely higher than placebo although there are small changes as we talked about before. I don't know why. We do have our clinical pharmacology colleagues trying to look at these data where it's possible, where they are comparing the other anti diabetic agents to placebo and trials where they had - where that kind of comparison is possible. Does that answer your question or?

DR. VELTRI: I'm just not sure what it all means given the fact that there is other common therapy that you alluded to.

DR. MAHONEY: Right.

DR. VELTRI: Therefore, the fact that there is a difference when you know, Liraglutide is not used, I'm not sure what it all means at the end, but I understand the limitations, thank you.

DR. BURMAN: Thank you, Mike. Let me remind you, we have five minutes before lunch. We will have time after lunch.

MR PROSCHAN: Okay. One of my comments is actually related to what you just said a few minutes ago about the relative risks are coming out bigger than one versus placebo versus you know, and not less than one versus the active comparator and on your slide 38, you list some possible reasons but you left off the most disturbing possible reason which is that the comparator was approved on the basis of HbA1c and not on the basis of clinical events and therefore, that could also explain why the rates versus I mean, so the comparator might have a cardiovascular problem as well. I'm not saying that this one does have a problem but you know, that's a possibility. The other thing was just a question about, actually it's to both the Sponsor and to the FDA, when you compared for example, some of the trials had more than one dose and when you compared so, I assume you took all the patients and all the doses and treated that as like a single trial rather than taking each dose versus the comparator group and then doing a stratified analysis that way. Is that - am I correct about that?

DR. DERR: Yes. Yes, you are correct. If a study had two or three dose groups, we would combine them together.

MR PROSCHAN: Okay.

DR. DERR: That's how you get the different allocation ratios.

MR PROSCHAN: Right and similarly, when you're comparing to all of the comparators in a single trial, you didn't treat each one of those as a separate trial but put them all together.

DR. DERR: Right.

MR PROSCHAN: Okay. Thanks.

DR. MAHONEY: I will say though that for the applicant's analyses that they did , they did examine by Liraglutide dose and there wasn't a relationship between dose and risk of MACE. They can confirm if that's correct by looking ...

DR. MOSES: I will just have our biostatistician confirm that for you.

DR. TU LE THI: Statistics. Can I have the slide with the chart, that chart of MACE? We looked - prior to our analysis, we looked into the different trials, how it looked dose by dose and slide on please. On this slide, you can see the proportion of subjects with SMQ MACE Population B and in the bottom you can see, the pool for the five Phase 3a trials and then the five Phase 2I trials split by dose and comparator and what you can see there, there is no dose dependency. So based on that, we pooled the doses when we did the analysis.

DR. BURMAN: Thank you. We will have time after lunch for more discussion with your permission, we will start with you and we will have discussion again with Dr. Wyne. We will go to you after lunch as well, with further questions and other questions as well. So, we will now break for lunch and reconvene at 1 o'clock.

(Lunch recess.)

QUESTIONS FROM THE COMMITTEE

TO THE SPONSOR AND THE FDA

DR. TRAN: Please take your seats. We will start in about 30 seconds.

DR. BURMAN: Why don't we get started for the afternoon session? There are no Open Public Hearing speakers. So, we're going to go right into questions, first from the Committee to the Sponsor and the FDA. What I'd like to do also is give an overview of the afternoon. I think there is going to be time limitations because there are a lot of things to discuss. That from approximately one o'clock to maybe 1:30 p.m., we'll have questions from the Committee to the Sponsor and the FDA, and then we'll go into a discussion of several questions, both on cardiovascular risk and thyroid issues, for the Committee spending about 20 or 25 minutes on each of those questions.

We'd like to finish off that discussion around 3:45 and go into the voting questions, of which there are several as well, which will take probably an hour or two to go through, vote, and explain the votes. We decided not to have a break in the afternoon because of time constraints, but feel free to get up, walk around or stretch as you deem appropriate. We'd now like to open the floor for questions for the Committee to Sponsor and the FDA, but I think the Sponsor has a short presentation of points of clarification from this morning that we had asked.

DR. MOSES: Yes, actually. One is the response to Dr. Teerlink if he is still interested in terms of receptor specificity and whether Liraglutide because of its different structure has a different receptor specificity. Is that still pertinent to you, Dr. Teerlink?

DR. MADSEN: Slide on, please. So, just for clarification, we did test Liraglutide against the number of different receptors and there was no binding to any

other receptors than the cognate receptor, the DOP-1 receptor. This is a list of the peptide receptors we've tested. There is a similar list of non-peptide receptors and I can let you know that they are all negative except the DOP-1 receptor. I don't know if it addresses all of your questions, but I have additional slides. Slide on please. I think this speaks more to sort of the binding of the GLP-1 analogues including Liraglutide to the human and the Cynomolgus monkey, in this instance, receptor. As you can see, there is a very similar binding pattern in the two species, and also as you can see there is very clear binding of also Liraglutide to the receptor. Did that clarify your question?

DR. TUTTLE: Thank you. The latter slide actually does address the main question. Thanks.

DR. BURMAN: Thank you.

DR. MOSES: One more - Dr. Burman, if it is possible?

DR. BURMAN: Sure.

DR. MOSES: Yes? So, the other issue relates to the mechanism of action in rodents and there seems to be some disagreement of interpretation between what the Sponsor has presented, what we have presented, and what the FDA has presented. We certainly agree that there are C-cell tumors in rodents, specifically in the rat, which has a high background rate of developing these tumors and we believe that Liraglutide and, as the FDA has already said, the class of GLP-1 receptor agonist is promoting growth of these lesions. I think it's important to recognize that there also may be evidence for other drugs that have effects on more than one species in terms of producing tumors and I'd like to ask Dr. Swinberg to actually come up and discuss that very briefly. Dr. Swinberg is Professor of Pathology and Toxicology, University of North Carolina.

DR. SWINBERG: Thank you, Alan. So, there was a statement, I'm sure that I've got the exact quote, but that there aren't any marketed drugs that are carcinogenic in both rats and mice and there is just a very recent publication that's come out, 2009 mutation research reviews, and if we could have slide NN72. This looked at genotoxicity and carcinogenicity testing of 472 compounds and what's shown on this slide are the carcinogenicity data and you'll see that there are 27 compounds that are positive in the mice and 30 in the rats and 15 of these are positive in both species.

So, this isn't such an unusual thing to have both rats and mice showing a positive increase in tumors. In fact, one of the drugs that's in this publication and is included in this 15 is gemfibrozil. This is a compound that humans have been exposed to for about 40 years. There is no evidence of human carcinogenicity and it's been looked for because it is a PPAR-alpha agonist and it's been studied in great detail. This is really very similar to what we're seeing here with the GLP-1 agonist because it's going to trigger that cell to increase in number and that eventually becomes a focal lesion and then a benign adenoma and then a carcinoma, depending on how long it goes on and what the exposure is. So, we've also heard that the new class of prolonged activation, GLP-1 agonists, are the ones that have this problem.

The fact of the matter is even the marketed drug was - its tox studies were done, as I recall, with a single administration per day. That's not the human exposure. It is exposure that is driving this response, but it's also exposure that gives you your clinical response for the therapeutic response. The humans and the monkeys absolutely do not respond to this agonist and that again is a parallel with the PPAR alphas because there's a difference there in the PPRE for PPAR alpha agonists that there's a difference in the sequence between the human and the rodent and that leads to this disparity between these

drugs. So, there are some well-understood mechanisms where we do have carcinogenicity in both species and they are non-genotoxic and it really is a promotion type of response.

DR. BURMAN: Thank you for that clarification. The FDA, yes, please.

DR. PAROLA: First I'd like to make a clarification that while focal hyperplasia and adenomas are common in rats, carcinomas are not and they occurred at low multiples of human exposure in the carcinoma studies.

DR. MOSES: They also occurred in the zero dose group although at low frequency.

DR. PAROLA: They are rare but they are not common.

DR. BURMAN: Hold on, please. Please finish your point.

DR. PAROLA: The Sponsor hasn't established a mode of action to show that the rodent carcinogenicity findings aren't relevant to human risk. They have shown, they have observational studies that these tumors might not occur in monkeys, but again, these studies use a small number of animals and expose for them for a short period of time. This, again, would be the first drug that causes C-cell tumors in two species, the same tumor in both species at low multiples of human exposure.

DR. SWINBERG: Yeah, let me just make one correction here, then I'll let someone else answer the last part of that.

DR. TRAN: Yeah, hang in one second for me, please.

DR. SWINBERG: Yes.

DR. TRAN: Yeah, please wait until the Chair recognizes you before you come up and speak. Thank you.

DR. BURMAN: Please.

DR. SWINBERG: Okay. The definition of rare is less than 1%. In this control group, it was 2%. So, it would be a common tumor.

DR. PAROLA: Yes, in this specific study, in one sex that's true, but the historical incidence, it's less than 1%.

DR. BURMAN: Dr. Moses.

DR. MOSES: No, thank you.

DR. BURMAN: Any other specific questions on that before we move on for other questions for the FDA and the Sponsor?

DR. KONSTAM: It's along this line.

DR. BURMAN: I think you are next is why -

DR. KONSTAM: Yeah.

DR. BURMAN: We're going to call you. So, please.

DR. KONSTAM: Yeah, I actually have one question along this line to the Agency and then I also have a question along a different line to the Sponsor. I guess we're going to struggle with this and I would appreciate hearing from the Agency a little bit more about, what is your general approach when you see a very concerning pre-clinical signal like this? We've heard a lot of debate about mechanism and I guess and I think there's disagreement about that, but I just would like to hear a little bit more about your approach. So, you see what you mentioned, two species, malignant neoplasm, concerning signal, red flag. What's your approach? How do you dissuade yourself from that signal? Is it possible to dissuade yourself from that signal on a mechanistic basis? To what extent do you really require enough clinical experience then to be sure that the signal is not in fact applicable to clinical experience? Maybe you could comment on those things.

DR. PAROLA: I'll comment on what we would consider evidence from non-clinical studies and maybe the medical officer might want to comment on the clinical issue. Uually if there - as in this case, if there are tumors at low multiples of human exposure in two species for the same tumor, this is the reason that the Sponsor did these mode of action studies to try and get at the relevance of this finding to human risk. The point of my presentation was to show that we don't think that they have provided us with a mode of action shown by these mechanistic studies to say that these tumors are not relevant to human risk. Whether they are clinically relevant, we don't, you know, I can't make that assessment from these studies, but we can say that their mode of action studies did not rule out the possibility that they might be relevant to human risk.

DR. KONSTAM: What I'm hearing you say, if I get it right, is that your approach to this would be to explore the mechanism because if you could be convinced that you understand the mechanism and convinced that that mechanism does not apply to humans, then you become less concerned. Is that a fair characterization?

DR. PAROLA: That's correct. That's exactly the reason that the Sponsor performed those studies.

DR. BURMAN: Marvin, did you have another point you wanted to make?

DR. KONSTAM: I didn't know if there was another response vis-a-vis, you know, do you want to see a certain clinical exposure to diminish the concern that the pre-clinical finding is real?

DR. PAROLA: Well, I could just make a general statement that the closer the exposure is in animals to human exposure that cause tumors, the more concerned, I guess, we would be, if there's not a mode of action to rule out human relevance.

DR. BURMAN: Thank you. Are there any further comments on that from the FDA? Yes, please.

DR. BRUNO: Karen Davis Bruno, pharmacology supervisor, DMEP. There are a couple of points I'd like to make. First of all, I think what you're hearing from us is that this is a multi species, multi gender, in essence a tumor that's rare that occurs at clinically relevant exposures. This is such a rare event that when the review team actually looked through the databases and looked through the relevant public databases, we found very few drugs which met this particular criteria.

Within our division, we have experience with one particular product, which was eventually approved, Forteo, which caused osteosarcomas in multi species, multi sex, at clinically relevant exposures, and that happened roughly four to six years ago. So this is an exceedingly rare event. We're concerned because it occurs at the clinical exposure. We're concerned because of the strength of the signal that's seen with Liraglutide for this particular tumor type and the fact that we don't really have mechanistic data in the animals that would allow us to dismiss the finding as being irrelevant to humans. So if we had a finding, for example, that could be monitored well in the clinic, we would be maybe less concerned, but this is a malignant tumor that's considered rare. It's rare in mice, it's rare in humans and that's why you're hearing the concern that you hear.

DR. BURMAN: Marvin, do you have one more question before I move on?

DR. KONSTAM: Well, I have on another topic.

DR. BURMAN: Do you want to hold on for a second and - sure.

DR. MAHONEY: I think really the key thing is that, you know, we do know that in animal studies at high multiples there might be other agents that have shown tumors in two species. I mean, for example, we know that Pioglitazone has a bladder tumor signal, but it's at very high multiples of human exposure and I noticed the slide that was presented a minute ago didn't give you the multiples of human exposure. So this is a very rare circumstance. I mean we looked very hard to see, to look for other examples. We also looked to see what happened. If we could see what happened when a drug such as this comes for consideration for approval, and we couldn't really tease that out. A lot of drugs that have multi species carcinogenicity signals are dropped during development and so we couldn't find very many examples that got considered for approval. All we can really tell you is that it's very rare for them to have been approved when it's a multi species, multi gender, at clinically relevant exposures.

DR. BURMAN: Thank you. We're still in this session for the next 15 minutes of questions for the Sponsor and the FDA. So, I think it's appropriate if the Sponsor wanted to make a comment on that.

DR. MOSES: Yes, I would. Thank you, Dr. Burman. As I've mentioned already, we believe that we have explained the mechanism, that is a GLP-1 receptor mediated event, and I believe the FDA has also supported that with their assertion that this is now a class effect with other agents being developed. Then the question is, how does this pertain to human biology? I mentioned earlier today that the calcium homeostasis and the role actually of both calcitonin and maybe native GLP-1 in modulating calcium in rodents is very different than the rat, but the most direct evidence, can I have - Paul, could you switch the slides please? Slide on. I just want to remind you that the other drug in this class, exenatide, which is in the marketplace and has been so

for the last number of years, has not in our animal models with continue as infusion been associated with the development of C-cell adenomas. There was no clinical monitoring of calcitonin in their clinical development program.

However, we have had the chance to monitor calcitonin levels and exposure to exenatide and Liraglutide. If in fact there is an effect of Liraglutide before of longer exposure, this is one example where one would expect it to be apparent. In this slide, both in the bottom panel and in the insert, you can see that there is no effect of either drug on serum calcium. Now this depends on the fact that calcitonin is a marker of C-cell activation. C-cell activation monitored either acutely or chronically through an increase in cell mass and we just see no evidence of that in this particular study amongst all of the other studies that we have performed.

DR. BURMAN: Thank you. Any other question on that particular point, before we go back to Dr. Konstam? Yes, please.

DR. PAROLA: I think that the effect of Liraglutide and GLP-1 agonist on GLP-1 receptor activation might be different than their effect on cell growth and cell transformation. So, I'm not sure that even though you didn't see a signal with Liraglutide in clinical studies that means that it's not having an effect.

DR. MOSES: With the Chair's permission, either you or Dr. Tuttle may be able to help on this. I think the validity of calcitonin as a marker of increased C-cell mass has been well validated in clinical practice. That's not just an acute effect but, as mentioned earlier, when we look at individuals who have elevated calcitonins prior to ever receiving drug (so, a more sensitive cohort of individuals) who have C-cells pumping out more calcitonin and administer Liraglutide to them, we see absolutely no effect.

DR. BURMAN: Thank you. Yes.

DR. SAVAGE: I guess, listening to all of this, I don't have sort of the technical expertise to comment on the various biomarkers and so forth, but I'd like to raise the question about - we're talking about a disease where people are likely to be taking a drug for 10 or 20 years if it works in them. We've got data that's only a matter of weeks in terms of the studies that we've been shown here. There are other drugs that can lower the glucose that aren't associated with this sort of problem and this sort of problem. If it's an undetected malignancy, is not a trivial problem. On the other hand, if screening or looking for it leads to unnecessary surgery, that's not trivial either. So, I think there's a reason to think carefully about how necessary it is to take that risk.

DR. BURMAN: Dr. Savage, thank you. Please bring that up again when we're on the questions later when the Committee is discussing. I think we have ten more minutes left for specific questions by the Committee to the FDA or to the Sponsor. Marvin?

DR. KONSTAM: I just actually want to pick up on Peter's comments. That was sort of a segway really to what I wanted to ask the Sponsor and hear also comments from the endocrinologists on the panel. When I see a safety concern or safety signal, I really pay a lot of attention to the differential value of the efficacy of a compound and I suppose if something was a novel treatment for a disease or a major incremental advance over a disease I might tolerate some risk on the other side. So, I want to get some more understanding of this. What I saw in your data was - in a number of the comparisons you had better glycemic control in comparators. I think the exception, if I'm not mistaken was the sulfonylurea.

DR. MOSES: Actually, there was better efficacy except in the combination of metformin plus sulfonylurea where the glycemic efficacy was equivalent, but there was a weight difference in favor of Liraglutide and a blood pressure difference and a reduction in hypoglycemia. So -

DR. KONSTAM: Okay. Well, I guess that's where I'm going. So, you know, you have apparent superiority to a number of other approaches. You have apparent superiority to a number of other approaches in hypoglycemic events, what may be relative to the degree of glycemic control although I didn't see a really clear analysis of that. You have the weight thing. I note that you're actually not asking for an indication about any of that, but I suspect that you'll want it in the labeling, all of that stuff. I guess I'd like to hear from some of the endocrinologists, either the consultants of the company or the people on the panel, and this really gets to Peter's point, how much of an incremental advance in glycemic management does this or could this drug represent at least to significant percentage of the population? Is this a major enough advance that maybe you would tolerate some safety concern?

DR. BURMAN: I think that's a question for the Committee to discuss, and we've seen the excellent data from the Sponsor. So, I think what I'd like to do for the next five minutes, with everyone's permission, is to move on to specific questions for the Sponsor or the FDA that they can answer and then we will have Committee discussion. We have three, Dr. Tuttle, Dr. Wyne and then Dr. Levitsky. Dr. Tuttle.

DR. TUTTLE: To the FDA, help me out here a little bit because I think we're going to end up in a situation where you're not going to be able to come up with a mechanism of action that excludes humans because we've got a ligand binding to a receptor that's on the C-cell. So, that's not going to be a great avenue of getting this drug

approved. I don't see how they can sort of go down that pathway. So, we're going to be left with some sorts of clinical studies. When you've been faced with this situation in the past, or similar, where you couldn't get a mechanism that explained it will never happen in humans, what sort of clinical studies were required to move it through the approval process? Have we gone down this pathway before?

DR. MAHONEY: Not really.

DR. TUTTLE: So, that's a problem.

DR. MAHONEY: Right.

DR. BURMAN: Dr. Parks.

DR. PARKS: I think I'll just add to the example of Forteo. As Dr. Davis Bruno mentioned, this is a very rare situation for the Agency to be faced with because again, for a lot of these cases here, the drugs are discontinued before they get to an NDA stage. In the situation with Forteo, and you're asking me to go back several years now the details may not be entirely exact, but it is a situation of looking at what is the benefit of that particular therapy, also in consideration of other classes of agents for that particular condition, and whether or not - and if we believe that benefit is very unique and will meet an unmet medical need out there, and then how we could not only label the drug but to target its use to the patient population where that benefit will clearly outweigh the risk.

For Forteo, they did not get approved on the first go round, but when they were finally approved, there were restrictions on its use, there were restrictions on labeling. So, it did get approved with a box warning, it did get approved with a medication guide. There was also contraindication in patient populations as well. So, I believe patients who had had external beam radiation, patients with elevations in alkaline

phosphatase, so, you could probably think about the patient population at risk in this situation. There was also a restriction in duration of use, I believe it was one year that you could use it. The endocrinologists are nodding so my memory hasn't failed too much. Then there was also - two years, okay. Then there was also - at that time it was called a post-marketing commitment.

In this day and age, we deal with post-marketing commitment and post-marketing required studies under FDAAA. The post-marketing commitment here was that a cancer surveillance had to be set up, a cancer surveillance is going to have to be set up, where the company had to provide to us updated data along with usage data so that we could get a sense of whether or not this background rate of a very rare tumor, whether or not there was any change with the availability of this product in the market.

DR. TUTTLE: Okay. One other question to either the FDA or the Sponsor; most of us don't generally perceive in humans C-cell hyperplasia as a pre-malignant condition unless the patient has a RET oncogene mutation. So, C-cell hyperplasia in and of itself in the normal thyroid does not lead to medullary cancer *except* C-cell hyperplasia superimposed on the RET oncogene mutation, which is a familial medullary. Is anybody aware of any data that that's an incorrect statement?

DR. BURMAN: Please. I have some data, but please go ahead.

DR. PAROLA: I think there might be a difference in terminology between humans and rodents that should be brought up. Focal hyperplasia in rodents, there are actually cellular changes and you can see these cells based on just Hematoxylin Eosin staining whereas diffuse C-cell hyperplasia the more numerous C-cells you would need to do calcitonin immunoreactive staining and quantitative analysis of thyroid tissue

to find that. So, I'm not sure if focal hyperplasia and adenomas in rodents that wouldn't correspond to carcinoma in situ in humans, but I don't know.

DR. BURMAN: I brought an article and I can't find it at the moment, but I will. It's from the Italian group, and I can spell that later and look the exact name up, where they looked at C-cell hyperplasia in humans and did laser dissection of 24 patients' thyroid glands, non-familial medullary thyroid cancer. So, it was C-cell hyperplasia due to various causes and then the laser dissection of the C-cells to identify them with RTPCR to see if there was RET positivity in those, implying that it was going to be oncogenic and progressive, and zero out of 24 samples had RET positivity in the nonspecific C-cell hyperplasia patients.

DR. PAROLA: Thank you.

DR. BURMAN: Dr. Wyne?

DR. WYNE: Thank you. I had some comments which I'll hold for our discussion so that we can stick to questions to the Sponsor or the FDA. A couple of the questions I had for the Sponsor, one, and I'm guessing since they haven't shone it, they don't have this, but do they have any data on bone markers or vitamin D levels in subjects in their development program?

DR. MOSES: I'm not aware that we have vitamin D levels. Have we analyzed the bone density data from the - we will try to find that for you Dr. Wyne. I don't believe we have a slide made up of that.

DR. WYNE: Okay. Thank you. My other questions, specifically they're related to the cardiovascular safety issue and what I'm struggling with there is the fact that the event rate is so low and this magic number of 1.8 was really set up on the assumption that we have a minimum number of events in patient years. So I'm trying to

understand why the event rate was so low in this population and wondering about that. Just if you have any information with respect to new statin use, statin plus fibrates, other associated what we consider to be cardiac related drugs such as ACEs, ARBs and so on?

DR. MOSES: Thanks, Dr. Wyne. We certainly have looked at the risk levels for this population. I'd like Dr. Zikman, our medical director for Liraglutide, to comment on that.

DR. ZIKMAN: If I could have the slide on. Specifically to your question about the statin use, it was rather high in this population. We calculated the percentage for the total population, placebo and active comparator ranged from approximately 40% to close to 45%. We also looked at the fibrate used, which was much lower. It was close to 10%. Then we also calculated for both statin or fibrates, so any hypolipidemic treatment. Then it was slightly more than 50%. Then combination of statin and a fibrate was close to 5% in patients on placebo. We also looked at it in a slightly differently way. Slide on please. This is the percentage of patients that reported hyperlipidemia as a baseline and here we again had the problem with the preferred terms from the MedDRA dictionary.

So we tried to pull the number of preferred terms that could relate to hyperlipidemia. They're at a number as high as 62% in the placebo group again. Then if we combine trying to define, so how many patients did really have lipid problems either represented by lipid-lowering treatment or reported hyperlipidemia, the number was rather high. It was 68% almost. Slide on please. Then trying to define the risk of the population, we tried to see, what would be the percentage of patients that either had concomitant cardiovascular disease reported at baseline or had a long duration of diabetes

or were at the age of 65 or had creatinine clearance that would classify them as being at high cardiovascular risk? Then the total number in a population was around 40%. I think this the best we could do to classify the population as per their cardiovascular risk.

DR. BURMAN: Thank you. Dr. Levitsky, question.

DR. LEVITSKY: The question was sort of answered before, but perhaps not answered in a way that I fully understood. The other drug that is available in this class would not be as useful for many patients as this drug, if it were to become available, because it needs to be administered several times a day. We have not heard of this complication except in the most general terms with the drug, which is now approved. Were the pre-tests done in a way which maintained the 24-hour levels? I mean are there any comparable pre-tests that would allow you to compare the available drug now being given two or three times a day to this drug? Do we know that? Are there data about that?

DR. MAHONEY: The information that the Sponsor showed was using a continuous infusion of exenatide and it's given by basically twice a day subcutaneous injection. I don't know of a way of comparing the two. What I can say is that we did look at all of the clinical trial experience for exenatide and in the clinical trials of exenatide there have not been any cases of thyroid cancer identified of any cell type, but they didn't routinely monitor for calcitonin. So, they didn't have this issue of more detection.

In post-marketing experience, there have been nine cases of thyroid cancers with exenatide and I believe three of those, I might get the number a little bit wrong, but I think three of them were identified as papillary and the others didn't have the cell type specified. Often you don't have a lot of information on spontaneous post-marketing reports. So, we don't really have a way to give comparable information for the

currently available drug. I would say though that when we mentioned that there are interim carcinogenicity data available for some other compounds, those are all GLP-1 analogues that are intended for once daily or less frequent use. So, they are long-acting compounds where we are seeing this question of the same signal in the animals.

DR. LEVITSKY: The one which is available, which is a short-acting compound, was not tested to give 24-hour comparability when it was tested in animals. So, we don't know what would happen if it were tested that way. I mean not with a short-term IV with infusion, but you know, weeks of -

DR. PAROLA: Actually, Novo Nordisk did some elegant studies showing that with multiple daily injections of exenatide there was no increase in focal C-cell hyperplasia in mice, but with sustained subcutaneous infusion, there was an increase in focal C-cell hyperplasia in mice. I guess if they'd like to elaborate further on the results.

DR. BURMAN: We really are going to cut this relatively short in a minute. Do you have a very quick comment?

DR. MOSES: The data are correct as stated. Continuous infusion does induce lesions in mice. I'm not sure there's any great advantage in showing the slide.

DR. BURMAN: That will be fine. Thank you.

DR. KONSTAM: What kind of lesions though? I mean -

DR. MOSES: We will show the slide.

DR. PAROLA: Focal C-cell hyperplasia, the tumor precursor lesion and it occurred within 13 weeks of dose -

DR. KONSTAM: So, I guess this -

DR. PAROLA: Not tumors.

DR. MADSEN: Slide on, please. I guess the study that's referred to, which is shown at the top here, is a continuous infusion study with exenatide dosed for around 12 weeks at three different doses and as you can see, there's a comparable study at the bottom with Liraglutide at the same or similar doses, and it's also a very similar dose, and as you can see, there are very comparable incidences of focal C-cell hyperplasia in these studies. We did not continue the studies until a duration that would make it useful or be meaningful to us or think there would be adenomas.

DR. BURMAN: Thank you. Ms. Killion, do you have a question for the Sponsor or the FDA?

DR. KILLION: Yes, thank you. I think this is what's termed a change up. As I was going through the materials, something kept coming to my attention and so I want to put that out there for both the FDA and the Sponsor and the question is this, if I'm a male diabetic, do I need to be concerned about using this drug more so than being a female diabetic? The reason I ask if there is a gender sensitivity here is because I have a note here that there's a higher instance of thyroid issues in males than in females. I don't know if that's true. I wrote that down.

DR. BURMAN: No. Most thyroid disease occurs more commonly in females -

DR. KILLION: All right.

DR. BURMAN: Including autoimmune thyroid disease and thyroid cancer.

DR. KILLION: Okay. So, there tend to be higher levels of calcitonin in males than in females just at baseline? Okay. There was a slide in here that talked about the dorsal subcutaneous carcinomas in male mice and that there are two factors affecting

that; micro-chips which I assume most humans do not have yet, but diabetics, I mean I'm looking at multiple subcutaneous injections, I was like, well, I think that diabetics, you know, at least the one using glargine perhaps do have some issues with respect to injections. So, again that's something that's in male mice.

Then the Sponsor's slide CE-61 talking about human C-cell histopathology findings, I'm looking at that and there's five males and one female. So, anyway, I'm sensing a trend here that there is information coming up with males and I just want to know if that's something that we should be sensitive to or consider or whether that's just sort of irrelevant?

DR. PAROLA: I can address the fibrosarcoma issue in male mice. Why it's gender specific we don't know. We don't agree with the Sponsor's analysis with regard to association with chip implants for identification. These fibrosarcomas were increased irrespective of the ones that were associated with the chip implant and the Sponsor in the histopathology report did differentiate between ones that were associated with the implant and ones that were not.

DR. MOSES: Dr. Burman, can I address that specifically?

DR. BURMAN: Yes, then we'll move on. Thank you.

DR. MOSES: Slide on please.

DR. MADSEN: Yes, I think you should note this figure, which illustrates how the mice were dosed, there are two places where they were dosed between the shoulder blades and on the rump, and then where the micro-chip is implanted. I think the red arrow sort of signifies the area where we saw the tumors. I think if you remind yourself of the size of a mouse, I think it's fair to say that this is within a very small area and not in any way comparable to the area in which diabetics have for injection. So, I

think, based on this and based on the fact that this was only seen at very high doses in single sex, we consider this of no clinical relevance.

DR. BURMAN: Okay. Yes, Dr. Mahoney.

DR. MAHONEY: I did look at non-thyroid malignant neoplasms also. There were 12 for Liraglutide treated patients and 5 for comparator treated patients, which represents about 0.3% and 0.2% of patients, respectively. For Liraglutide, there were four prostate and two breast and the others were single cases of cancers of a variety of cell types, none of which were sarcomatous. Just what we know from humans.

DR. PAROLA: Would it be possible for me to show a backup slide that I had? Slide number 45. This shows the incidence of fibrosarcomas on the dorsal surface of CD1 mice. According to the histopathology report from the Sponsor differentiating between the fibrosarcomas that occurred on the skin and subcutis at the ID chip implant and the injection site, these incidences are shown as percentages. So there was significant increase of the skin and subcutis fibrosarcomas in high-dose males.

DR. MOSES: We don't disagree with those data. The comment was that it's a very small injection area and the concentration at the highest dose. It's the same volume administered at all doses, but the concentration is very much higher, obviously, at the highest dose.

DR. BURMAN: Thank you. I apologize to everyone ahead of time because obviously we're not going to have enough time to discuss everything in tremendous detail, but we do need a thorough discussion and do need to go through the questions. It's 1:45 about now, and we want to go through the questions over the next two hours until 3:45 and then at 3:45, go into the voting questions and actually vote. So, if my math is correct, that leaves 120 minutes of about six paragraphs, six questions to go

over. So, about 20 minutes each question and some of them are going to take longer than others. I will also mention that we've decided to discuss the cardiovascular questions, the thyroid questions, and then vote on the cardiovascular and thyroid questions at the end because we wanted a full discussion of both of the issues before we actually voted. We're not going to vote on the cardiovascular question immediately after discussion of that section. So that having been said, what I'd like to do is open the floor for Committee discussion on the question number one. Sure.

DR. KONSTAM: Sorry to interrupt you, Ken, but the thing that I just am concerned about, you know, reading through the questions, none of the questions, as far as I can tell, specifically addresses issues of efficacy. The reason I want to come back to this, as a cardiologist, I'd appreciate getting a better sense from people who treat diabetes a lot, about the degree to which they think that the efficacy that's been shown in the clinical trial portfolio represents a major new advance. That's something that I don't have clear in my mind from the data and I'd just like to hear some discussion about that from people who know more about it.

DR. BURMAN: Thank you. It's mandatory we go through these questions, but it's also important to discuss relevant issues. We only have 120 minutes to go through the questions, but I think it's a relevant enough issue you brought up for five minutes for any of the diabetologists on the Committee. Dr. Wyne, would you like to address that succinctly?

DR. WYNE: Yes, the efficacy actually is quite good for an agent. The A1c lowering is a very nice level of A1c lowering. Again remembering it's add-on or in combination. The one thing that this drug does give us that we feel, we were talking about this, is that it's a once a day dosing and even though we always say, well, our

patients are used to twice a day, everything they do is twice a day, we still know clearly from data, that once-a-day dosing has better compliance than twice a day.

So, having a medication, even though it's an injection, it's once a day, you don't have to check your sugar, you just take your injection. It does not cause hypoglycemia, those are points that are very important to patients. As I said, the efficacy is nice. It's not one of those borderlines where it's barely making 0.4% decrease on A1c. What we're seeing typically is 1% drop. In other words, if you take your typical patient in the US who has an A1c in the 8s, you may get them to at least the minimal goal of below 7% with adding this on to their current regimen.

DR. KONSTAM: So, to follow-up, I mean you say it's nice. Is it nice enough that at least in segments of the population you would administer it accepting some risk? I don't know if you could sort of give an answer to that?

DR. WYNE: The answer is yes. Remember too, we have this huge resistance on the part of patients and healthcare practitioners to add insulin onto therapy. This is an alternative to add on to their oral agents to have a chance to get a person at least below 7%, and again minimizing hypoglycemia and weight gain, which are the two biggest issues patients are concerned about.

DR. BURMAN: Anybody else on the Committee, as an endocrinologist, wants to respond to that? Ms. Killion?

DR. KILLION: Well, I'm not an endocrinologist, but as a patient, I have to second everything that Dr. Wyne just said. Once a day beats twice a day, hands down. Low incidence of hypoglycemia or low risk, excellent. Weight loss, phenomenal. I mean these are things as patients, we all want to see. With any drug, we're evaluating risks all

the time, but I have to say from the patient perspective, I'm pretty excited about this agent and this class of drugs in general.

DR. BURMAN: Dr. Veltri.

DR. VELTRI: Yeah, my other - similar to Marvin, I want to try to get what this drug would potentially do more than hemoglobin A1c. So, the proportion of patients reaching target on top of the comparator, the weight loss is important, but what about the blood pressure and some of the modest lipid effects? Is that above and beyond what current therapy would allow you, not just the hemoglobin A1c control?

DR. BURMAN: Dr. Wyne.

DR. WYNE: So, in the data in diabetes, actually blood pressure lowering has a greater impact on macro-vascular, but from UK, PDS has an impact on both macro-vascular and micro-vascular disease and when you look at large meta-analyses, small decreases in blood pressure potentially have a great impact on outcomes. So that is potentially clinically relevant even though we don't have enough outcomes here to be able to show a clinical relevance to the decrease in blood pressure. Definitely with respect to the occurrence of microalbuminuria and the progression of microalbuminuria, any amount of blood pressure lowering is beneficial there. What was the other parameter? Oh, lipids.

I was curious of what their baseline lipids were. They told us there was a beneficial effect. Triglyceride lowering in diabetes is very problematic. So, I believe they said they do have a beneficial effect on triglyceride, which would be wonderful. Raising HDL is also problematic in diabetes. So, anything that does that is nice too. We take it as a given that everybody with diabetes should be on statins to get LDL to goal, less than 50% of these people were, but even adding them on to statins is not going to get

triglyceride and HDL to goal. So those other benefits, even though we don't have direct outcomes, would be viewed as a positive reason to want to add this on to your current regimen.

DR. BURMAN: Dr. Mahoney, do you want to respond and then we'll move on to the questions?

DR. MAHONEY: I just want to say that we didn't present information on our efficacy evaluation today. I'm not the efficacy reviewer, but I think I can speak fairly generally that we have evaluated the primary endpoints and the A1c data do seem to be pretty much what has been discussed. Perhaps the data on having a small weight loss is correct, but all of these other secondary efficacy endpoints such as blood pressure and lipid effects, we cannot, at this point, validate that the applicants conclusions are supported. So just keep that in mind, if you're thinking about balancing efficacy and safety, we think that you can believe the A1c data and you can probably believe the small weight loss data, but we are not yet ready to say that we can fully support the other secondary endpoints.

DR. BURMAN: Thank you. We're going to move on to the questions and thank you for bringing - oh, I'm sorry Dr. Parks, I didn't see.

LISA: Hi, I'm Lisa. I did the clinical efficacy review. I just have one additional comment about efficacy, about the claim of superiority for two other trials. Just to remind you of the trials they did. Your slide 16 - just to remind you of what the comparisons were. So, there were three trials, and please correct me if I'm mis-stating, but there were three trials that you were able to look at superiority over another anti-diabetic drug. In the two that you found superiority, I just want to add the caveat that the

superiority of rosiglitazone, we want to caution that the dose used was actually only 4 mg, which is half the FDA maximum-approved dose.

Thank you. The other trial that you claim superiority for was the comparison to glargine and I have in front of me the rates of success. So, the glargine was titrated to a point. I thought that the success rate to reach that target was actually notably low, 40% for less than 120 fasting plasma glucose and only 20% for those patients who reached the target of less than a 100. So, we have to be careful again in claiming superiority over glargine when glargine is based on titratable effect and that effect wasn't necessarily reached.

DR. MOSES: Just one comment to that and then I think we'll get the Chair back in control here for the questions. The issue is that glargine was used as it's used in clinical practice and the problem with insulin, basal insulin or any insulin, is that titrating to that target, and it is the target is challenging because of the risk of hypoglycemia. So, beating that in a clinical trial where we are actually pushing patients to a target with a specific titration regimen, I think is actually very much of a plus.

DR. KONSTAM: Can I ask the - just -

DR. BURMAN: No, no, we really have to move on. In case you didn't remember, I'm a retired Colonel. We really do have to move on and I apologize to the FDA and the Sponsor and the Committee members, but it's mandatory we go through and have a further discussion of these questions. So, maybe some of these further issues will come up, question number one, which will raise further questions.

CARDIOVASCULAR SAFETY

POINTS FOR DISCUSSION

DR. BURMAN: Discussion Number 1 is on the screen. It says:

Discussion No. 1

Please discuss whether the low cardiovascular event rate in the Liraglutide clinical trials permits a reliable assessment of cardiovascular safety. I'd like to open that question up for Committee discussion. Marvin.

DR. KONSTAM: Well, I think it's problematic. I think this Committee is now getting used to these different endpoints and I've begun gravitating toward the more specific ones on the list, for example, the FDA custom. The number of events we're dealing with that drive these point estimates and confidence limits is pretty darn low. Looking for example at custom MACE population A, if I've got it right looking at the FDA slide number 40, we're talking about 26 events total in the active drug and comparator arms together. I think we've seen - so, there is that.

The point estimates tend to be below unity, but the confidence intervals are large and I'm sort of feeling that in fact those confidence limits actually were sensitive to the analytic approach that was taken and that coupled with the fact that these were not pre-specified or adjudicated and such, in my mind, as we talked about yesterday, sort of broadens what might be the real confidence intervals. So, all of that put together, I think the event rates that we have are problematic in terms of getting to definitive evaluation.

DR. BURMAN: Thank you. Dr. Teerlink, you are a cardiologist, do you have any further comments on that?

DR. TEERLINK: Well, It's nice to hear that from Marvin. I would agree with what he said. I think also one of the things that I'm interested in, and I don't know if this is kind of stepping out, but since yesterday we had talked a lot about patients who had had diabetes for at least ten years' duration seeing, well what were the effects of the

agents in those patients? I would have been interested in seeing that analysis here as well. One of the things that I'm very concerned about is that we still are dealing with just such small numbers and supposedly, this is remarkable, you guys were able to enroll 25% of the patients who had diabetes for at least ten years and yet you were able to achieve an event rate that's even lower than the previous groups.

That's quite remarkable and I think one of the best prognostic signs for patients with diabetes would just be in one of these trials, and they won't develop cardiac disease and that's true in I say that partly in jest because obviously that is true across the board in clinical trials. Patients who get in the clinical trials were generally very healthy, but we have just such a small number of events here, and in this example, there is clear dynamism in the confidence intervals as well as the point estimates and I think probably the most relevant experiences in the placebo versus your drug comparison. That's where you have such few numbers that the confidence intervals are huge including at sometimes 5 to 10 times increases in event rates. So, I do not have confidence that we have been able to exclude significant cardiovascular effects in this case.

DR. BURMAN: Anybody else? Mike?

DR. PAROLA: I also think Dr. Wyne made a good point earlier that the criteria of 1.8 that was really tied to a certain minimum number of events and it's kind of problematic because if you have very few events, or a medium number of events, showing that the relative risk is 1.8, you'd still have a relatively high relative risk and pass and on the other hand if you have a huge number of events, suppose you had a million events, and suppose the true relative risk was 1.5, with a million events the confidence interval would be very narrow and again you'd rule out 1.8. That's why they have built in - part of it is you would also need to see a reassuring point estimate. So, I

think in the long run, I think the criteria could probably be improved. I have some ideas on how that might be done, but it's hard. I think the comments that have been made so far are correct, that it's hard to be really confident with the data in the small numbers that we've seen.

DR. BURMAN: Anyone else from the Committee want to comment on that? Dr. Wyne?

DR. WYNE: I would like to, again, compliment the FDA and the Sponsor for all the work they've done to try to dissect out cardiovascular events realizing that these studies were completed before this issue was raised, before the guidance was issued, and they've really done a lot of work and a very nice job to try to dissect this. I share his comment that I'm very impressed with how low the event rate is in this population, and in general these people have had diabetes on the order of about 7 to 9 years. So, I would start to expect to see more events. The reason I was asking about associated drugs was to try to get a sense of how high risk these people are. Unfortunately, there is just not enough events to be able to say definitively other than to say, again, if you are characteristic of the people who are in these studies, it seems to be very safe, but the people who were excluded from these studies, we truly don't know anything about the safety and we're just going to need more data to answer the question ultimately.

DR. BURMAN: Dr. Joffe.

DR. JOFFE: I have two questions - one comment and one question. First, I've heard a few people mention a minimum number of events that need to be had when looking at this goal post of 1.8, and I just want to point out that the guidance does not specify a certain minimum number of events.

The second point I want to make is looking at custom MACE population B, 21 events with Liraglutide and 17 with total comparator. I add that. That comes up to 38. Yesterday, we were talking about 40 events. So, it sounds like there's a bit of a difference today in terms of what we said yesterday. The actual number of events is very similar.

DR. TEERLINK: Actually, I think I've been pretty consistent.

DR. KONSTAM: Can I comment on that?

DR. BURMAN: Sure.

DR. KONSTAM: Well, there is a difference that we haven't brought to light, which is the difference, the acceptability of the follow-on population as opposed to the primary population. So, this really hasn't been brought out up until now, but - I guess I don't know how much we should talk about yesterday's meeting, but in another meeting that we all attended, we saw although there was a long-term and short-term, in that case the long-term was maintenance of randomization and blinding. Big difference here as I understand it, is the blinding goes away after you move out of population A. So, that plays on my thinking, which is why I here tend to gravitate more to population A. I don't know how other people feel about that.

The other thing is that I take your point about how important is the event rates. So, I think I share John's and others comments that I do care about the event rates because I believe the confidence intervals more when I have more events, but also the difference is that we're dealing with upper confidence balance here, depending on the analysis method, they get pretty close to 1.8, and we didn't see that in the other meeting that we all attended. So I think it's the aggregate set of issues; the number of events, where these confidence boundaries actually are falling, where the point estimate is

actually falling, this issue about the lack of blinding in the follow-on population, are all different from the application we saw yesterday.

DR. BURMAN: As I mentioned earlier, we're going to go on this particular question until 2:05. Mike, you had a question. Then please make it succinct.

DR. PAROLA: Okay, yeah. No, I agree that guidance doesn't call for being tied to a certain number of events, but the Advisory Committee meeting on which that guidance was based did mention in reference to a specific number of events. So, I think that the guidance really should be changed somewhat.

DR. BURMAN: Dr. Rosebraugh, yes.

DR. ROSEBRAUGH: Just a real brief comment on that. I agree with what you say. There was a minimum number mentioned. That was with the idea of how many events do you need if you have a point estimate of unity or an unfavorable point estimate. We really didn't discuss what you would need to see if you had a favorable point estimate. It was more to give a sense of how difficult would it be for Sponsors to make these goal posts.

DR. BURMAN: Two more, hold on. Ms. Killion, you had a comment?

DR. KILLION: Very briefly. I just wanted to build on what Dr. Joffe was saying, is that my sense of it in a non-clinical lay person's point of view is that the goal posts are moving a little bit today and I just want to be very clear that what we're being asked to assess and the difficulty of proving negatives and the fact that this study like others we've dealt with are in this interregnum period. So, I just want to try to focus in on and keeping the criteria similar and not imposing extra scrutiny.

DR. BURMAN: Dr. Veltri.

DR. VELTRI: My comment would be simple in that, yes I agree these are low cardiovascular event rates, but for those of us that are designing actually prospective clinical trials with patients with very high risk atherothrombosis, these folks have really very good background therapy, aspirin, ACE inhibitors, ARBs, statins, etc. and it's almost every day you hear about a trial which has had to increase sample size because blinded aggregate event rates are lower than anticipated. So, I think that's overall good for healthcare, but it makes it a lot more difficult to discriminate, such as here, where this was not pre-specified and what have you. Just a comment.

DR. BURMAN: Marvin, you had one quick comment?

DR. KONSTAM: Well, first of all, what I was going to say is that I do think that I pick up on Rebecca's comment from yesterday that one size doesn't fit all, and here is, I do think, an important point, which is in my mind, if I felt that this was a major incremental advance in diabetes management then I for one would be more accepting of greater uncertainty about the cardiovascular risk. I think that plays in here although that's not specifically asked in any of the questions. I'm unsure about exactly how much of a major advance this was, but if I was convinced that it was a major clinical advance in diabetes management, personally, I would tolerate more uncertainty, which I think is what we have here, compared to yesterday's application.

DR. BURMAN: Thank you. What I'd like to do now is an impossible task of summarizing the discussion and see how close this is. Part of it is related from yesterday as well, is that we're dealing with low events with non-adjudicated events over relatively short-term and trying to make assessments of cardiovascular risks. The numbers, as I look at them, say that they do meet the goal post of 1.8 for the vast majority of the studies they did, especially with regard to total comparator whether I am being

favorable on that regard, but are above the 1.3 cut-off suggesting that if we went by the strict guidelines, without the other considerations mentioned, they would meet the guidelines, but would also have to have post-marketing studies. We have to be careful about the interpretations and the lack of long-term studies in the small number of events.

Others on the committee have made the discussion and emphasized the fact that the small number of events makes it very difficult to make long-term studies and Mike has made the discussion as well, the comment that an upper limit of 1.8, still is difficult to interpret in this particular context. I think in regard to efficacy, everyone has to make up their own mind, but that's my overall summary of this.

Any major arguments or disagreements?

(No response.)

I realize these are difficult issues. We will now move on to question number two, which is a longer question on the board.

Discussion 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 Liraglutide development program was already completed by the time the Guidance was issued. For Liraglutide, 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 and was not designed to prospectively measure cardiovascular risk associated with Liraglutide. Please discuss whether these endpoints and in 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 diabetes programs that have already completed or had ongoing Phase 3 programs at the time the Final Guidance was issued.

We're going to go on this question and we did discuss this yesterday as well, until approximately 2:25. Does anybody on the Committee have any further comments? John.

DR. TEERLINK: Well, so, I think we'll just re-emphasize that as much as they can, people who are currently in this interregnum period should try to do these analyses and I've asked for it in this meeting and this other unnamed meeting. To actually see these event rates for this higher risk group, I think other Sponsors should be required to show that and try to say, "Okay, if we look at what could be a higher risk group, to give what the events are, what the possible effects of their agent are in that higher risk group."

So, you need high-risk patients, you need to get better events and as has been done in other trials, I think external blinded evaluation of those few events that are there needs to be also performed. So, that would be helpful as well. I think the Sponsors also, I would caution future Sponsors on being careful about, on the one hand saying, "Oh, well, these are small numbers so we can't pay attention to them", for example, we didn't really talk about this, but in terms of pancreatitis risk, which is an eight fold increase in this study with this agent, we don't talk about that because that's a small number, but we're going to be confident that this agent is safe in patients with coronary events with numbers that are essentially about the same in terms of absolute numbers, not the ratio. So, that will be the advice for future Sponsors.

DR. BURMAN: Let me ask Dr. Savage, did you want to make your comment now?

DR. SAVAGE: Well, I guess if I understand what we were talking about earlier, it seems to me that one of the problems we have is that we have only a very vague concept of exactly how representative the populations are that we're being asked to look at in the data from this meeting and from the other meeting and others, and before that, and how they correspond to the population of patients that are likely to receive these drugs. Admittedly you need a group of patients that are treatment naive or at least can be treated with monotherapy to find out if there is any particular short-term toxicity associated with the new agent.

You don't want that confounded with some complex drug regimen where you don't know what happened. In addition to that you need a group of patients that are more like the general diabetic population that the Sponsor wants to get approval to use this drug in. It would be nice to have some way of scoring cardiovascular risks so that there could be a graphic showing how the population that's being presented to justify the approval of the drug corresponds to the population of diabetics that are out there, that are likely to be using that drug. The data for the diabetics could be got from a national database or form some large HMO database or something where there would be enough data to get a pretty good estimate of what risk factors would be like in people with a certain duration and so forth. So it would be helpful because it would give us some more quantified sense of what the comparability of the data sets that we are looking at are.

DR. BURMAN: I think that's a good suggestion. Dr. Wyne, you had a comment?

DR. WYNE: So the question of, is really, what here is useful? What can we say about the things that have already completed their studies? So people who are not in a position to be setting up more studies or maybe they should be setting up more studies. I'm with Dr. Konstam that as he said nicely he is gravitating towards liking the custom MACE. I find custom MACE is much more helpful than the SMQ MACE. I would say from things that I have heard from the whole panel that this elevated CPK is not helpful and it's distracting. I think that in terms of trying to understand the risk of the patients and to understand a little bit better of who had events some things would be useful to us by telling us who had events within the context of baseline A1c and duration of disease? I mean specifically not just saying, 'oh they weren't significant'. Those are parameters that we think of as predictors of CVD risk.

Also knowing about their baseline lipids and where the people who had events the ones with the worst lipids those would help us understanding how it relates to the population. One thing is maybe correlated to in ACORD type of group, which actually they did do. They showed us on questioning that about 40% of the people were at increased risk. So that kind of showing the data a little bit differently for parameters like that will at least help us to understand what happened with the higher risk people.

DR. BURMAN: Okay. Alan, Dr. Moses.

DR. MOSES: I just for, Dr. Teerlink we did look at - and if Dr. Wyne the number of individuals who had diabetes greater than 10 years to do a MACE analysis was done last night I can't speak for all validation. The Custom MACE population A had an odds ratio of 0.39 for those individuals with the duration greater than 10 years. The confidence intervals were broader because this is a sub-population.

DR. BURMAN: That's fine and there is smaller number of events the, that I could make first.

DR. KONSTAM: Well I just want to say that, you know, about looking - so you have got a population that generated a small number of events. You can't get from here to there by doing subgroup analyses with that, okay. So and, you know, because all you are going to - because it's a game of event numbers. What you are going to do at the end is shrink the numbers. The advice for future studies and future Sponsors as let in patients, you know, with who are likely to or have established adverse thoracic disease. In this application I think the Sponsor went a certain distance to exclude those patients, including excluding patients with prior myocardial infarction and so you wind up with your events and I think those patients in the future have to be let in.

DR. BURMAN: Dr. Teerlink.

DR. TEERLINK: So in fairness to the Sponsor, you know, my point actually it was not - actually I didn't care about the point estimate. So you should go ahead and be, I think it's appropriate for you to go ahead and be allowed to tell us what is or the confidence intervals with that.

DR. MOSES: The confidence interval was up to two on that one but the range was 0.08 to two.

DR. TEERLINK: Right. The point is actually that you are - the reason I would do this one I'm actually agreeing it's just to make it very explicit that when you actually look at a population of interest, which is for me a population that's actually at risk for the events that within that group we really have very little confidence that we know whether this is safe or not. That's actually why I would suggest that and if a

Sponsor can show that confidence and that's great and that will actually go further for me being comfortable.

DR. BURMAN: Dr. Veltri.

DR. VELTRI: Maybe I misread the slide but I thought the Sponsor actually showed the slide where if you take at least from a univariate perspective those patients and their database who are over 65 or at greater than 10 years or training clearance less than 60, I think that was a fairly sizable number of patients in the entire database. So I think in fairness to the Sponsor I think they did try to at least identify patients who potentially could be at higher risk obviously there may have been some patients excluded, you know, with MI or lower ejection fraction what have you. I would be interested to know if they have, what that point estimate confidence interval was for that.

DR. MOSES: We have not done that point estimate it's correct that it was over 40% of the population but it was not point estimate. This is exactly the population, we described or I described this morning for the post approval hopefully outcomes trial.

DR. BURMAN: Any questions by anybody else on the committees who – anybody else Dr. Teerlink you had another comment.

DR. TEERLINK: Well you had mentioned that, you know, it's important to have that these cardiovascular trials have that the event rates getting better and better. I don't know if many cardiovascular trials that have an event rate that's below - so considerably below 1%. So I think we are not seeing the kind of events that at here plus these only 30% of the patients were on statins. All the therapies that you said were important for showing improvements and outcomes are not being used to the extend that

we see in most contemporary cardiovascular trials and despite that they still have an extraordinary event lower event rate.

DR. BURMAN: Any other comments by - or questions on this question.

(No response.)

Let me try to summarize this question because really what the question asked is offering suggestions or improvements to the endpoints in analysis that maybe applied to other similar diabetes programs. This is summary that we recommend that there is still a higher risk group perhaps including as mentioned yesterday renal failure people with high cardiovascular risks that there certainly be a blinded independent evaluation and adjudication of cardiovascular events that we have raised the question whether data applied in a low risk group applies to high risk groups. We do agree that they should compare, broaden the comparison of the generalize diabetic control groups and that we agree that the Custom MACE seems to be more specific as it gets rid of the issue of elevated CPK, which seems to be more nonspecific. We would also like to relate the cardiovascular risk parameters to drug response. Anybody have any additions or modifications to that summary.

(No response.)

All right and let's move onto question three, which we will spend until about 2:40 p.m. or 2.45 p.m.

Discussion No. 3

In the cardiovascular event analyses, a primary comparison was made of Liraglutide to total comparator (active control plus placebo). Subgroup analyses were also conducted for Liraglutide versus active control alone, and Liraglutide versus add-on placebo alone. The recent Guidance for evaluation of cardiovascular risk for diabetes

products does not specify that the 95% confidence interval upper bound limit of 1.8 must be met for subgroup analyses. Results were similar for Liraglutide versus total comparator, and Liraglutide versus active comparator. However, comparisons to placebo were sensitive to analytical method, often yielding point estimates greater than 1 (not favoring Liraglutide) and often yielded 95% confidence interval upper bounds of greater than 1.8. Analyses were stratified by study, and lower baseline risk did not appear to contribute. Please discuss the relevance of these differences noted by type of comparator to the Liraglutide program, and the role of these separate types of comparators in the evaluation of the cardiovascular risk for future diabetes drug applications.

This question is now open for discussion. Mike?

DR. PAROLA: Yeah. I mean I think this is a huge issue because as I have said, a lot of the drugs for diabetes were approved on the basis of HbA1c lowering and therefore, we don't know whether these other drugs that, you know, you are comparing yours to, or might have a problem with cardiovascular events. So, you know, I think it is troubling that when you look at it versus placebo the relative risks are coming out bigger than one. I don't know what the way to handle that in the future is. I think it is very difficult. I think it's got to be unfair to someone no matter what. I do think it probably should state, if you are going to use the criterion of 1.8, you know, I think, it should state that, that's relative to, you know, something specific, you know, may be what you could try and do is to estimate, what the relative risk would be to placebo. I do find it troubling that it's sort of a floating comparator and it's not made specific, although I don't know exactly how to fix it.

DR. BURMAN: Thank you. Anybody? Katherine?

DR. FLEGAL: Yeah. Just to follow up a little bit on what Rebecca said before. We are getting in a situation where the goal posts are kind of moving because now we are talking about sub-group analysis and about having criteria that are getting harder and harder to meet. That's kind of a necessity because of the small number of events, in a way, but there is a temptation to start trying to dissect those and look at yet more sub-groups. I don't think that was, that really is making it more and more difficult to meet the criteria's we apply in that way, it is moving the goal posts.

DR. BURMAN: John.

DR. TEERLINK: Yeah. I think I disagree a little bit with that in as much as I don't think we are really moving the goal post, I think we are trying to get the best estimate of where the ball really is relative to the goal post to continue the analogy. I think it is appropriate to look at different groups, the reason we look at the sub-group analysis is because of this potential concern that the other comparators may be different and may behave differently. It's not necessarily a neutral comparator. Our best, I think all of us would agree the best estimate of the true risk of this agent is going to be reflected in the placebo group. The problem is there are few events there, there are even fewer events there. What would have been nice is if they had kind of all lined up on the same kind of side and then we would and sure we could have probably been okay with the different confidence intervals, but the movement of the point estimate as well as the marked increase in the confidence intervals, I think makes it a little bit more challenging but I think it is useful to take that into consideration.

DR. BURMAN: Maybe I can ask the FDA, either Dr. Mahoney or Dr. Joffe, you had mentioned yesterday that you consider the best, maybe even today, that considered the best comparator is the total comparator group, not just the placebo alone.

DR. MAHONEY: I don't know that we would say that one is better. I would say that the guidance doesn't specify that you have to meet this particular upper boundary for our sub-group analyses.

DR. BURMAN: Thank you. Ms. Killion.

DR. KILLION: Okay. Here is another change-up. I will, those of you who have been on panels with me before know that I am a little bit sensitive to sort of the overall diabetic condition being hijacked a little bit by cardiovascular concerns. What I want to point out is, you know, we need to be looking at in addition to our cardiovascular risk, again as we discussed some other time ago, the diabetic population is very diverse. Treatment for, we are talking about Type 2, which can have an onset very young where the cardiovascular risks are not as prominent in certain of the segments of the population. So of course we need to assess this risk and we need to stratify our concerns about this drug. Let's not throw the baby out with the bath water, let's take a look at the fact that we have a significant lowering in hemoglobin A1c, which for diabetics in general, has been the target and it will continue to be the target. Let's just keep that in our minds as we are discussing these other things and not let the perfect be the enemy of the good.

DR. BURMAN: Thank you. Dr. Veltri?

DR. VELTRI: Yeah, in regards to the placebo, I think we are really fooling ourselves here because, you know, diabetes now is a CHD equivalent. I don't see how we can maintain patients on placebo for any period of time. They would, by definition, if you could do a placebo control trial, be low risk. So that would be defeating ourselves and if we are trying to enrich our understanding of benefit for both microvascular and macrovascular disease, I think that the comparator analysis would allow longer term and more events because by definition they would be at higher risk. So

it would be nice if we were back then and do placebo control trials, but I just think, you know, we are where we are today. It's much more difficult to enroll such patients and I think it's a difficult situation to be in but I don't see how it's feasible from a Sponsor perspective or from a clinician's perspective who are seeing these patients to keep them on a placebo for a very long time.

DR. BURMAN: I agree. Marvin, did you have a question?

DR. KONSTAM: So, I think the sub-analysis of the placebo control group is a pretty darn important sub-analysis. I think the usual standard for active comparator findings as Mike alluded to is really to try to attempt to impute what placebo would have looked like because the standard is effectiveness versus placebo, risk versus placebo. However in this case, I guess I have to agree with Rick. I am actually very comfortable with the overall comparator group, including the active comparators.

As Rick pointed out, you know, you can't have your cake and eat it too (which I shouldn't be saying at a diabetes meeting) but, you know, if we are going to get events, you are going to have to follow patients for a long period of time and the ethical imperative will be to manage their diabetes. The problem being that we don't really know, we don't know the cardiovascular effects of all the comparator drugs and that's a problem but the reality is that we are going to add a new therapy to existing therapies and the reality is, I think it's very worth comparing the cardiovascular risk of that agent to, you know, what they would be on if they didn't have that drug. I think in this case that's a pretty reasonable approach.

DR. BURMAN: Dr. Mahoney?

DR. MAHONEY: I just wanted to reiterate one thing. The trials which used a placebo comparator were not monotherapy trials in naïve patients. They were

add-on trials where you had a certain baseline diabetes therapy that was standardized and you either added placebo or active drug to that underlying therapy. So they weren't trials where patients were maintained only on a placebo for any period of time.

DR. BURMAN: Thank you. Dr. Wyne?

DR. WYNE: This issue of placebo versus active comparator, I understand the comparisons. Dr. Mahoney explained them. It makes beautiful sense to me. I still get confused by this issue of placebo because I keep seeing this in diabetes studies in the evaluations that somehow when you compare to a placebo, whether it's add on to active therapy or true, nothing at all. Somehow you don't seem to have as much benefit and this keeps coming up in glucose related studies and I've never understood it. I don't know that we ever will understand it. What I do know is from a reality clinical perspective, I would not treat a patient with a placebo and if I feel their A1c is not at goal I would not add-on a placebo, I would not do nothing, I would take some sort of action. So to me from a clinical day-to-day perspective the comparison to the active comparator is more realistic and related to what I am going to do with my patients and hopefully my colleagues will be doing.

DR. BURMAN: Thank you. Any other comments?

(No response.)

What I would like to do now is summarize question number three, which was the bottom line is please discuss the relevance of these differences noted by type of comparator to the Liraglutide program and the role of the separate types of comparators in the evaluation of cardiovascular risk for future diabetes drug applications. I think that the panel has a consensus that the comparators were all agents approved for treatment of diabetes and had efficacy with regard to lowering A1c and that their potential effect on

cardiovascular events hasn't been studied precisely, that the total comparator probably to me seems the best overall relative group to compare to and we have had discussions of placebo and these are placebo add-ons where there is much more variation in the statistical analysis.

The guidelines don't discuss specifically analysis of what should be done or analysis of sub-group studies so it is up to each group individual to decide for themselves how much they want to take into account the larger variation in the greater upper limits that were found in the placebo group as compared to the total comparators. I think that's my summary anybody want to add to that?

(No response.)

Discussion No. 4

All right and the fourth one I think is more specifically statistical. Fourth question, which is 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.

I think this was illustrated today in the varying responses we saw. Mike you probably want to respond to that?

DR. PAROLA: Yeah but actually I want to sort of tie that back to this 1.8. I know, I don't want to keep harping on this. I do think there is one thing that you could do in addition to just looking at whether the confidence interval excluded 1.8 or not. So what you could do, my suggestion would be given the number of events in each of these trials what you could do is you could calculate the probability of passing that criterion given that the true odds ratio is say 1.5. You could calculate the probability of passing if the true odds ratio is 1.4, etc. That would help to sort of figure out whether you think

you've met the burden or not. I think that's an additional piece of information that would be helpful for me to do. You can do an exact test for that because you're conditioning on the totals in each trial. So you could do an exact test and figure out what the probability of passing that criterion is.

DR. BURMAN: Could you explain that just to a non-statistician just for a minute, Mark?

DR. PAROLA: No. Yeah what I am saying is, they have the criterion that you must demonstrate that the relative risk say, or the odds ratio or whatever you want to demonstrate, is less than or equal to 1.8. I am saying that criterion is a little bit questionable and it would help me if I knew what the properties of that procedure were. So what I want to know is, given the number of events that you have had in each of these trials, what's the probability of passing that criterion if the true odds ratio is a certain thing?

So if the true odds ratio is 1.7 for example, I would be reassured if the probability of passing that criterion is low because to me 1.8 is not the real, you know, what I want is a procedure such that, if the true odds ratio is say 1.5 or better you got a low chance of having the confidence interval be less than 1.8. So want I am suggesting would sort of be a way to evaluate the properties of this 1.8 upper confidence interval boundary. It would help reassure me if I saw that it had good properties, namely a low chance of passing if the true odds ratio is something high, like 1.6 or 1.7, and a high probability of passing if the true odds ratio is 1.1.

DR. BURMAN: Any other comments by the committee on the statistical question?

(No response.)

No. I won't even attempt to summarize that at the end. You did a great job and we agree.

All right what we would like to do now is move to the next question. There are two questions left. These are now regarding thyroid. We expect some controversy here and will go to until about 3:00 or 3:10.

THYROID TUMORS – POINTS FOR DISCUSSION

Discussion No. 1

Please comment on whether the applicant has provided adequate data that treatment-related thyroid C-cell tumors in carcinogenicity studies of Liraglutide are rodent-specific and not clinically relevant to humans as part one of that question. Then part two is the clinical issue, which we would like to address separately, 'include calcitonin findings from clinical trials in the discussion. Let's focus on part one of that for the moment, which is the rodent related tumors. Is that unequivocal? Is that suspicious? Mike, do you have a comment on that?

DR. TUTTLE: Yes. As I said, we are trying to put all of the pre-clinical data and the clinical data in my head. Here's the best I can do. I think we can't dismiss the rodent data when you have two species and two genders that have C-cell tumors, an unusual circumstance it has to be addressed. I don't think we can rule out any effect on human thyroid cells because C-cell receptors clearly - GLP receptors are present on the C-cells. The drug binds to the C - cells. What we don't know is the effect of that binding either on calcitonin, on growth stimulatory, or on any kind of carcinogenic effect. Since the drug binds to the receptor I don't see how we can dismiss out of hand that there couldn't be an effect. It looks like to me do we actually have two models in the mice.

One model that is a susceptibility model to developing medullary cancer is the rat. Because the rat has a higher pre-disposition anyway, it has a higher background rate, it changes over time. One model would be, that's very similar to my familial medullary patients that have a RET gene that's present and when you stimulate their receptor maybe you see more action and activity.

The other model is the mice; very low likelihood of developing spontaneous C-cell problems and much less likely to develop it in response to the drug. That's much more akin to my average patient that I see without a genetic predisposition. So rather than trying to merge the mice and the rats together we may think about them as sort of two different scenarios that we would have to deal with, which gets us into sort of risk factors about which patients may be more at risk from developing problems with this.

The other thing I would point out is that if we decide to use these drugs and somebody gets C-Cell hyperplasia and then develops medullary cancer they are very, very unlikely to suddenly develop lethal medullary carcinoma. This is a slowly progressive disease. It's picked up on ultrasound. It's picked up on physical exam. So just the finding of a medullary cancer would not be life threatening. It would certainly be a big deal and it would need to be treated. It's not like we would be creating generally a fatal disease that was out of control.

DR. BURMAN: Thank you. As a thyroidologist, I would like to make some comments as well. I certainly agree with Mike's comments and it seems to me that there are - the critical issue is whether non-familial medullary cancer occurs as a progression from C-cell hyperplasia to medullary thyroid cancer in patients who are RET negative and that answer, unfortunately, is unknown. As I discussed, the article from

Italy before suggested that RET negative non-familial medullary cancer does not progress necessarily to thyroid cancer but that largely is unknown. We haven't mentioned as well the fact that calcitonin comes from other sites besides the thyroid gland. I have a whole list, which I won't go through, of multiple other tumors that can elevate calcitonin, including all neuroendocrine tumors including small cell carcinoma of the lung, which can be quite lethal. Dr. Becker has published articles showing that, if I remember correctly, 30 to 50% of patients with small cell carcinoma of the lung have elevated serum calcitonin levels and yet we don't have any information in humans regarding any other - the presence of hyperplasia or tumors in any other site. We are only focusing on the thyroid gland here. Further, there are other markers besides calcitonin that can be used that haven't been bought up.

They include CEA and pro-calcitonin. There is an article this month in JC&M talking about the increased enhanced value of measuring pro-calcitonin rather than calcitonin in patients with medullary thyroid cancer. I think the issue also is, in humans is the Liraglutide increased calcitonin levels significant? and do they return to normal? and I agree with what Dr. Tuttle said earlier that the rises in calcitonin are very minimal. Two-percent of the patients had a rise greater than the normal range. We are dealing with unknown issues as to what's the likelihood that that really is related to further development of medullary thyroid cancer. I think those for the moment are my major comments.

DR. TUTTLE: Thyroid guy to thyroid guy. He probably regrets teaching me years ago. The other issue I think that's really important is that this hyperplasia syndrome in adults is no big deal. We see hyperplasia in the thyroid 30% of the time; we see it in response to proton pump inhibitors. We see low level of calcitonin. So, when

we are thinking about bad endpoints that we want to avoid, C-cell hyperplasia isn't necessarily one of those. There's a little difference in the rats when we deal with that focal C-cell hyperplasia. The only place we see focal C-cell hyperplasia in the adult population is in those genetic same RET mutations where the focal C-cell hyperplasia is a precursor. So I think this concept that if we cause C-cell hyperplasia, I am not necessarily sure that's a good thing or a bad thing. It certainly is not automatically given that it's pre-malignant because the majority of the data out there says we see very, very few patients with medullary carcinoma compared to a 30% of the population with C-cell hyperplasia. So I think the preponderance of the data is that diffuse C-cell hyperplasia is *not* premalignant and that if that's all that we cause and we make the calcitonin go up one point, the risk is essentially nil and now the benefit may outweigh the risk. So when we are looking at endpoints I think we have to sort out whether we are talking about just causing hyperplasia or whether we are causing real medullary carcinoma of the thyroid.

DR. BURMAN: We don't know that. It's really an unanswerable question based on the data at the present time because obviously all patients who received this agent are not going to have a thyroidectomy. So we happen to have a small number of patients, one patient, with medullary thyroid cancer in the Liraglutide group and four to five patients who were operated on because they had elevated calcitonin and then had papillary cancer, but you don't really know how many we're missing because it's frequently an indolent disease and might take years and how do you study that either in a pre-marketing or post-marketing condition when it takes so long to develop disease?

I would also mention that smoking, Hashimoto's thyroiditis, Sjögren's disease, and PPIs as well as neuroendocrine tumors, just to name a few, all cause transient, non specific elevations in calcitonin. Yes.

DR. PAROLA: I would just like to comment that although rats do get this progressive disease from diffuse hyperplasia to focal hyperplasia to adenomas and carcinomas, the molecular pathology is not the same as in humans. They are actually RET mutations. Activating RET mutations have not been identified as a cause of that in rats and so Liraglutide is unlikely to act through a RET dependent mechanism in that setting.

DR. TUTTLE: I agree. You probably predispose it, there was something in that RET C-cell that predisposed them to adenoma or that progression. It may not be RET, but just from a theoretical construct there's some other driving gene that predisposes them. That adding on the receptor stimulation would add to that.

DR. BURMAN: Anybody else on the committee?

DR. KONSTAM: So I have nothing intelligent to say about medullary carcinoma of the thyroid, but, I think I can speak to the situation that the panel and the Agency is in, seeing a very concerning pre-clinical signal and I guess having, you know, been burned on panels like this before where attempts at a worrisome signal of some sort, whether it be pre-clinical or in a surrogate human finding and writing them off on mechanistic grounds, I think is hazardous.

You know, in this situation, frankly, the only thing that would make me comfortable is if there was prior experience with this particular pre-clinical signal in drugs that have had sufficient human exposure to test some of these mechanistic hypotheses and know that yeah, we have seen this before and it's not a problem and here's why. I would say, respectfully, to the mechanistic concepts that have been put forth by the Sponsor, that I think they are theoretical, they have been questioned by the Agency. Again, in the absence of prior experience with moving into the human

population and seeing a non-problem, I would be very weary of accepting that as a reason to write off the pre-clinical signal.

DR. BURMAN: John. I'm sorry. Dr. Wyne was first. Sorry.

DR. WYNE: I actually just want to make a comment, but before I make my comment, to what you were saying - one thing to keep in mind is the Agency does now have enhanced tools to ensure that further surveillance is done, they really do have the ability to make sure that proper studies were done for this class and I think that we can trust that looking ahead to the future and it is important to think of this is a long-term thing because we are now keeping people alive from their cardiovascular disease and diabetes so that they can get other complications.

The comment I have about this issue is more of a general conceptual thing. If you look back in the endocrine literature 30 plus years ago when this entero-pancreatic axis was proposed, where the incretin came from, they also proposed an entero-thyroid axis. The idea was the gut is making hormones that talked to the C-cells and said, hey a load of calcium is coming, get ready. So, so maybe this is part of that axis. So the question is, is it possible that maybe this is an appropriate physiological response.

Now appropriate to what and why? I don't know. I do know that people with diabetes have a lower bone density, maybe they need that calcitonin to maintain their bone density or to help it out, but we are worried about this C-cell hyperplasia for the reasons we have talked about, but in these same patients these compounds cause, Islet cell hyperplasia and were not distressed about that Islet cell hyperplasia and in fact, it hasn't been an issue previously for this class because we are so happy to have it to get the increased insulin secretion. So I find it interesting that it may be a similar parallel endocrine process and I understand why we are worried, you know, because cancer is a

serious matter, but we don't know enough about the physiology and it may be that there is a – there is a teleological reason for all of this and we need to consider that possibility

DR. BURMAN: Thank you. I think Dr. Teerlink was next.

DR. TEERLINK: So I am still, as a cardiologist, trying to figure this thing out. So there seems to be the C-cell hyperplasia pathway that develops over time and might or might not lead to eventual cancer and then there's these other kind of more like a two-hit type thing where you have an underlying RET mutation that then can transform relatively quickly without having going through this calcitonin elevation thing, but the calcitonin is more of a response to the transformation than a cause there, is that?

DR. TUTTLE: Yes, sort of. No. In the familial RET oncogene type, it's the RET gene that's the driving mutation, they drive through C-cell hyperplasia into medullary carcinoma of the thyroid. So that's the sequence to finding those guys.

DR. TEERLINK: Right. So it seems like in the rat, that's not the mechanism, it's not through that RET pathway.

DR. PAROLA: Correct

DR. TEERLINK: So we have a signal in two animal models that we think is not similar to the signal that we think we understand in humans. So it doesn't seem like we understand whether what was happening in the rat and mice can or cannot happen in the humans. Is that reasonable?

DR. TUTTLE: That's an absolutely true statement. I can't rule it out, but mechanistically it certainly doesn't rule it in.

DR. TEERLINK: No, but we do see it in two different species and so given that there's lots of homology in many humans or rats, etc, I am just concerned that

because this is a relatively unique compound we may be developing this and being able to trigger it.

DR. BURMAN: That's it, Dr. Parola.

DR. PAROLA: Yeah, there has been no proof that Liraglutide activates the RET pathway in either mice or in rats and causes the tumors via that pathway.

I had a second comment. Even though GLP-1 agonists do cause beta cell hyperplasia in rodents it doesn't cause pancreatic cancers or beta cell cancers in rodents until your studies.

DR. BURMAN: Rebecca, yeah, Dr. Henderson.

DR. HENDERSON: So in the clinical trial when they showed the six people who had thyroidectomies the reason given was elevated calcitonin, but yet a lot of the conversation is how calcitonin is irrelevant and as the consumer representative I need to have this explained in laymen's terms, talk to me like I am a first grader, non-science, no statistics tables, how do you reconcile that given reason is elevated calcitonin for thyroidectomy, but yet it's not important?

DR. BURMAN: Calcitonin, the degree of elevation is important in that normal is up to 5 or 10 picograms grams per mil. The sensitivity of picking up medullary thyroid cancer when the value is greater than a 100 picograms per mil is extremely

DR. HENDERSON: In laymen's terms

DR. BURMAN: Oh sure, sure. You said first grade

DR. HENDERSON: Normal first graders.

DR. BURMAN: Sure. The calcitonin normal level is less than 10 picograms per mil and when somebody has a value in the range 10-20-30, probably up to 50, most of the time it's non-specific and usually is not associated with medullary cancer

but is due to one of these other factors, whether it's a PPI or they have Hashimoto's thyroiditis or something like that. Once the value is over 100, it's very specific for picking up medullary thyroid cancer. That is why there's so much debate about whether the calcitonin level should be used for screening. So here we are talking about very small elevations that the Liraglutide causes, that were only in 2% of patients were twice or above the upper normal range, if I remember correctly, or above the normal range. That still is a very low level, if the normal range is up to 5 or 8, we are talking about levels of 10 to 20. In the individual cases that they give, the patients who had medullary cancer had levels that were usually high.

So the bottom line is if the value of calcitonin is above 50 or 100 most people will recommend the surgery, lower levels are much more controversial and so it's – it's a good marker when it's high, it's not such a good marker and it's non- specific when it's low.

DR. HENDERSON: Wouldn't small incremental levels get you to 100 eventually?

DR. BURMAN: Well, that's the whole question. The Sponsor presented evidence that the levels went up and then went down and that, further, people who had elevated calcitonin levels at the outset and were put on Liraglutide, the levels remained stable and didn't rise.

DR. TUTTLE: From a simple clinical perspective, most people who have calitonin in a 10 or 15 don't have disease and it never changes and it's important to them because they are going to worry about it, their doctor worries about it and so it leads to a thyroidectomy. So when we say important, what we are talking about is finding clinically important disease. All this little micro-medullary we accidentally found by

taking out these thyroids, we didn't save anybody's life. We found little disease that would have probably never been clinically significant, so when we talk about clinically important it's what we really mean, not sort of important to an individual person.

DR. BURMAN: I respectfully disagree with that last comment, Mike, in that small papillary cancer is probably irrelevant in the majority of cases. Small medullary cancers that are really medullary cancer, not C-cell hyperplasia, are thought to be more potentially aggressive.

DR. TUTTLE: Then we will disagree.

DR. BURMAN: Dr. Levitsky.

DR. LEVITSKY: So I'm asking a question which is only one step up from the lay question. I have a vision, I am trying to figure out how one could feel that we can't really answer this question, which seems unanswerable, yet feel that this is a good drug and yet it needs surveillance and then we set up in some way to create a surveillance system in which patients getting this drug also get their calcitonin checked every so often without turning this into the Thyroidologist and Thyroid Surgeons Full-Employment Act. This is what I am wrestling with, I don't know how to – I don't know how to do this right and maybe someone else has given more thought to this and figured out a way to do it.

DR. BURMAN: I think it is very difficult to decide either in further pre-marketing studies or post-marketing studies how you are going to pick up this C-cell hyperplasia clinically or the medullary cancer that's there because it takes a long time to grow, the markers are relatively insensitive at these low levels. Dr. Wyne or Dr. Tuttle do you have further comments?

DR. TUTTLE: Eventually somebody was going to ask that hard question and I was trying to avoid it. The issue really is if we send everybody in this room out to get calcitonins done, a lot of people are going to have a high number and we are going to have to take their thyroids out. Secondarily if you say, well, we can't approve this drug until we know it causes medullary, even in the example we have been talking about where we have RET oncogene, a very powerful driver oncogene, except for the unusual cases they don't get C-cell hyperplasia until they are teenagers, they don't get medullary until they are 35 years old and in the lighter mutations that don't drive as hard, they don't get medullary until they are 70.

So, you know, if we contemplated having to wait until we had people data on this, it will be my children's committee. I have real concerns about using calcitonin or ultrasounds for screening, for exactly what you talk about. If we do it, we are going to have to set some very high number of calcitonin, below which you try to give the physician's permission not to work it up although that will be very difficult because if it's 0.1 above the normal range it's going to lead people to ultrasounds and scans. So I struggle with knowing how to do that.

DR. BURMAN: In fact Mike, let me just follow-up on that. What do you recommend either in pre-marketing or post-marketing studies for follow up and monitoring of these patients regarding C-cell disease?

DR. TUTTLE: Before this morning, I pretended it didn't happen. Life was easy, now I got to go back and see patients tomorrow. I am not internally sure. I think in all likelihood, if it was my daughter I would probably measure her calcitonin before I started her on it. Although I know how to interpret a calcitonin, I am not going to get real excited if it's less than 50 or 75, but I have concerns about recommending that

to the general population where I know every value 0.1 above the normal range leads to evaluations. Remember these are adult diabetic patients. Half of them will have nodules on their ultrasound, 50%. So even if you screen with an ultrasound it's going to lead us down that pathway. It's hard to me though to envision, you know, doing this without following some sort of calcitonin parameter, Ken. I think we just need to set the number high enough where it's clear, that it's not one point above the normal range means you have C-cell hyperplasia, but we also don't want somebody ignored with a calcitonin of 1000 and put on trial.

DR. BURMAN: So just on this important point, you're in favor either pre-marketing or post-marketing of having a screening test before someone gets put on this medication? For calcitonin level? and how often would you measure it?

DR. TUTTLE: I used to like you a lot. First you need a good history. So clearly if they have a family history of medullary carcinoma or a personal history of medullary carcinoma I think that would probably take you off and then I guess with this concern I would want to know what my patient's serum calcitonin and was before. I am convinced based on the data, we are not seeing tremendous changes over a year or two. So yearly follow up would probably be adequate and there's no data from the clinical thing that we change any faster than that.

DR. BURMAN: Of course, I know, obviously, I realize the dilemma here and we are discussing a very common disease with perhaps millions of patients on it, that you are now recommending serum calcitonin screening for this issue.

DR. TUTTLE: If it turns out there is no signal in five years I will probably have hurt more people than I helped. If it turns out that this drug really is

causing C-cell hyperplasia and medullary then I have probably helped more people than I hurt.

DR. BURMAN: I know we have more questions, but let me just follow up on one thing. Are you also saying that certain select, I would say a certain select patients shouldn't be put on this drug, if somebody has a family history of medullary cancer, they shouldn't be put on this medication.

DR. TUTTLE: Yes, correct. Right now until we know more, if somebody has a family history of medullary carcinoma, MEN type syndrome, familial medullary carcinoma, probably familial pheo-chromocytoma, those folks should probably not go on this drug. Or a personal history of medullary carcinoma.

DR. BURMAN: Dr. Flegal. Did you have a question?

DR. FLEGAL: No. It's been covered.

DR. BURMAN: Dr. Veltri?

DR. VELTRI: As you can say, you know, we are dealing here with ascertained bias versus ascertained risk in a way. Obviously we don't want to subject patients to thyroidectomies and what have you unnecessarily based on calcitonin level per se unless it's very, very high. One of the concerns I have though here is trying to put this dilemma in perspective.

How does one ascertain what the truth is? Obviously we are in a bind here because as the FDA said, there's two species both genders, you know, exposure, risk. Yet there may be clinical benefit on a very serious unmet need in diabetes. I guess what would one do? I mean the Sponsor has recommended pharmacovigilance, claims database assessments, but those are association and doesn't necessarily prove it and in the clinical trial proposed it's 9000 patients perhaps. Remember here, as I understand the

data, there's only 10 thyroid cancers albeit in 4,000 patients exposed versus not exposed to five years which a clinical trial would be, but there's only three medullary carcinomas of those. The others are papillary. So even at the end of the day with the pharmacovigilance up, that's going to be undertaken in the projected clinical trial I am not sure you are going to get an answer. So it's one of those uncharted territories with an uncertain return either and I guess getting back to what Marv is saying, you know, what is the benefit risk? Is there something about this on a diabetes side that potentially can offset a potential risk?

DR. BURMAN: Thank you. Dr. Savage, you had a comment?

DR. SAVAGE: Yeah, I want to come back to my – my question about what are the trade offs? It seems to me that obviously one of the advantages that's been mentioned is that this is a longer acting drug and involves less burden for the patient. One of the other things that was brought forward as an advantage is the ability to get the glucose under better control with less risk of hypoglycemia, although the detailed data on that issue is not, I haven't seen enough to be totally convinced of the magnitude of that benefit. Theoretically it could be very important, but I don't – either I have missed it or I haven't seen it.

One of the other issues, which I don't think the data are available for yet, is how long does this benefit in terms of stimulating insulin secretion and so forth last? It lasts for the period that these short studies have shown us, but it hasn't indicated whether it's something that if a person is put on this drug and kept on it for 5 or 10 years, will they really be benefiting all that time or will it be the third drug of some combination that they are taking? So, I think there are questions that we don't know the answer to in terms of the benefits and then it's still somewhat unclear to me how much of a burden it will be on

a patient because it sounds like, and I may be misunderstanding this, but it sounds like there are going to be people having thyroidectomies that otherwise wouldn't have needed them and so forth, and that's not a trivial thing. You can get hypoparathyrodism or something as a consequence. So I am concerned that I have not yet seen sufficient evidence of a major benefit to feel that the trade off is positive. I wonder what other people think about that.

DR. BURMAN: Dr. Parks, you had a comment?

DR. PARKS: Actually, it is a question to Dr. Tuttle and you, Dr. Burman. Is there already an established registry for MTC or are these patients being followed by the cohort of thyroidologists who came out of Walter Reed?

DR. TUTTLE: The answer is no. There is not a particular cohort. Medullary carcinoma patients tend to congregate to sort of big centers because they are an unusual center so they tend to cluster around several major centers, but they are taking care of all over the United States. They have a very, very powerful web group, the medi web group, this message is probably already out there on the medi web group, so the message gets passed very quickly through that group of patients. No, as far as I know there's no real prospective established registry where you could find all the medullary patients in the United States.

DR. BURMAN: Me either, Mike. Let's see, Dr. Felner?

DR. FELNER: I just had a question from earlier. I don't know if I missed it. Did the Sponsor give the data on those with medullary carcinoma thyroid? If they were RET positive or not? I don't know if I missed that or if you didn't present it.

DR. MOSES: We did not present that data and again the one case had a markedly elevated calcitonin at baseline of over a 1000 pico grams per mil. The other was a microscopic diagnosis based on a marginally elevated calcitonin level.

DR. FELNER: So you didn't assess, so that wasn't assessed.

DR. MOSES: I'm unaware of those data

DR. BURMAN: Dr. Teerlink.

DR. TEERLINK: I'm just picking up on Peter's comment which I think that was really quite cogent and really, really helpful. One of my concerns is this trade off between the risk benefit, I think it's what we are all trying to struggle with. One of the potential things that could come out in this trial of 000 patients is, we will be starting that trial saying, you know, we are a little concerned about this thyroid thing, we are going to watch it and we will get a sense from that trial how often people get their thyroids taken out.

We will get a sense of what the actual risk is in a controlled setting and actually have a real live comparator group. So we will be able to assess well, what is the additional risk? What is the additional kind of trade off in terms of that? Also be able to follow patients for concerns about thyroid related complications from those interventions. So that is something that we might get more information on through post-marketing or pre-marketing depending on where we put the evaluation.

DR. BURMAN: As we said that's difficult to know how to monitor those patients. We recommend calcitonin levels and maybe other studies, and occasional sonograms as well. Dr. Konstam.

DR. KONSTAM: I just want to agree with everything that Peter said a moment ago, I think he said it really well and I think that my message to the Agency is,

when considering the approvability of this compound I think it would be, to me, illogical to accept the degree of uncertainty of risk that we have in front of us around this particular issue without clarifying the offset of that, without clarifying the degree of superiority that is offered, at least in subsets of populations of this agent vis-à-vis the clinical efficacy. We asked that question earlier, we sort of see some signals in that effect, but then I heard from the Agency that we are not so sure about that and we are not so sure we are going to get any of that into the labeling. Then I would just point out, to me, it would be very illogical, you know, to accept this degree of uncertainty of a major risk without some very clear suggestion that it's an incremental advance in clinical efficacy.

DR. BURMAN: Dr. Levitsky.

DR. LEVITSKY: So I don't know, as a diabetologist who takes care of a fair number of young type 2s, I would say that that's a no brainer. Insulin makes you hypoglycemic and fat. Metformin, lots of people can't take because it makes you sick to your stomach and the pills are too big, and the other drugs have all sorts of potential complications associated with it. So, yeah it would be an incremental advance if it worked the way it looks like it does. I don't think that, that takes much thought actually.

DR. KONSTAM: Can I just say, if that's really true then I would say, maybe this degree of risk can be accepted and tolerated and managed. I mean, that to me is the critical trade off here because I don't think you can make the uncertainty around this go away and so I think, I'd love to hear whether other diabetologists really feel that strongly because if that's the case, I think that would have a major impact on my assessment of this risk.

DR. BURMAN: As an endocrinologist, I would just like to weigh in. I think that the medication is efficacious based on hemoglobin A1c and fasting blood sugar, but I don't think it's revolutionary or offers tremendous new advantages. I think it will be of benefit, but there are other medications available as well. Everyone has to decide for themselves how much benefit it will be. I do think it's a good agent that is efficacious, but it's very difficult to weigh the efficacy versus the potential problems. Anybody else? Mike.

DR. TUTTLE: I don't treat diabetes so I can't really speak at all to the efficacy piece of it, but in terms of the risk what we have to remember is the risk is not somebody suddenly developing medullary and dying in a year. We've got one and two year follow-up, we've got people on Byetta. The risk is, are they going to develop years down the road, medullary carcinoma of the thyroid? While it's never good to have cancer, we are not really talking about something that's going to suddenly pop and kill somebody in six months or a year. So we are trying to balance the benefits of improved diabetes management with the potential risk of something that might happen years down the road that is probably manageable and treatable. It's not none, but it's not sort of, this risk of developing a cancer and dying in six months.

DR. BURMAN: Thank you. Ms. Killion.

DR. KILLION: Yeah again from the patient's perspective I have to second again what Dr. Levitsky said. In terms of efficacy, in terms of having another tool in armamentarium, it's very important. A lot of diabetics do not want to take insulin. A lot of diabetics, I think that was pointed out, are very resistant. Having something that you can take once a day that doesn't have the risk of hypoglycemia, as somebody who has had severe hypoglycemia, it's not fun, and let's not forget that people die from

hypoglycemia as well and that is an event that takes place very quickly, not over time, and it can't be monitored. I mean there are no, you know, diabetics deal with risk every day, lots of risks. So, you know, this is a risk that has to be managed. The question is, is it a manageable risk? Not, is there no risk? Not, is there a really elevated risk? Is this something that a diabetic can live with? From a diabetic point of view I think if you can get improved hemoglobin A1c, if you can have something that helps you control weight which has to be a benefit from a cardiovascular perspective as well, if you have something that is a manageable protocol that's a very important consideration for a patient who has to deal with this every day for the rest of their lives.

DR. BURMAN: Thank you. Dr. Wyne.

DR. WYNE: I think what we're struggling with is we don't know the natural history of this process. I don't want to say disease, I say this process and I was glad you asked Dr. Tuttle the question of should we measure levels because I didn't know the answer to that either. What I do know is that the data from the Sponsor suggest that the calcitonin levels are very small and the changes are very small. So as a global population I don't think their data supports that we should be checking everybody. I was hesitant to mention this, but Dr. Tuttle mentioned exenatide and we do have quite a bit of patient-year experience with that and I guess the question would be is, maybe at least from the coding data, is there any data to suggest an association with a C-cell carcinomas? I mean, is there any data there? It's imperfect, I agree. So then what do we do with our patients?

Well, Dr. Teerlink raised a very important point which is there is a prospective study that will be done if this agent is approved. Personally I think it's going to require a lot more than 9000 patients, but from this perspective that is a good thing and

there can be something built into that design to look at this more closely. What about our patients though, in day to day life? Well first of all when you are taking care of someone with diabetes you should be feeling their throat at least once a year, if not at least at every visit and if you feel that you feel something abnormal when you feel their throat, you should be sending them for an ultrasound or doing it yourself if you have the machine there. So that question raises should we then automatically measure calcitonin? ATA says no, but apparently the Europeans say yes.

I downloaded a paper from an American journal yesterday that proposed we should be doing so and they felt it was cost effective. So maybe that's the point where we could say we should be measuring a calcitonin if we feel something on exam. In terms of the absolute levels, there comes this issue of 50, 100, what about the idea of looking at trends in the calcitonin and also associated medications. Most of my patients with diabetes are on H2 blockers or PPIs. So that's going to be very problematic to look at absolute numbers, but maybe we could propose looking at the natural history of the trends and maybe that could be done in this large study that's coming. I am just raising some possibilities of things we can think about to go at this question because we don't really know what the natural course is here.

DR. BURMAN: Of course, measuring a trend implies that you would measure at least two values. Not related to these patients, but doubling time of calcitonin is a marker for thyroid cancer and aggressiveness, but not in this circumstance. So you are suggesting that maybe patient measures several samples over a period of time

DR. WYNE: Over their lifetime, if I can keep them alive long enough.

DR. BURMAN: Yeah and Dr. Levitsky?

DR. LEVITSKY: I guess my question for the thyroidologists just would be, that it was my understanding that although our hands are fantastic if we are endocrinologists and we really can feel those thyroid nodules, we might not be able to feel them early enough with medullary carcinoma so that the hands on and then the measurement of calcitonin might not be the way to go, you really want to catch the tumors.

DR. TUTTLE: Yes, the best way to catch the tumors is just go ahead and take the thyroid out. That makes it easy. It's a little tongue in cheek. A couple things to clarify. The ATA guidelines actually say there's not enough evidence to recommend for or against calcitonin testing and the evaluation of nodules. So we actually come down in the middle, recognizing that there's data on both sides. So that's why they come down. In terms of actually following these patients. If somebody has a calcitonin of 30 they might have C-cell hyperplasia they might have a little medullary carcinoma of the thyroid, they are not going to have clinically significant medullary carcinoma of the thyroid. So when you are doing the follow up, I think there's no way we can exclude subtle C-cell hyperplasia, we are not going to be able to find one millimeter medullary carcinomas of the thyroid, but if you follow that trend over time you will be able to find clinically significant disease that's likely to be important in the patient.

DR. BURMAN: As you mentioned, palpation is certainly the most insensitive method for picking up tumors. Dr. Levitsky, and then we'll go over here.

DR. LEVITSKY: Is there a level of calcitonin that you could feel fairly sure is not going to be associated with metastasis or with spread of the medullary carcinoma beyond the thyroid that is likely to cause someone to have a very slow and

uncomfortable death? I mean, that's the real question, what is the level that you would choose?

DR. TUTTLE: Yeah, the level is a little bit arbitrary because it sort of depend on the patient's own calcitonin, but a couple of good numbers to hang around; if the calcitonin number is more than 100 then the likelihood that you have medullary carcinoma is very, very high. As it gets less than that, it gets lower and lower. Most people with aggressive medullary cancer, that die of medullary cancer, you don't need the blood test to find it, you feel it in the neck, they have palpable lymph nodes, their chest x-ray is abnormal.

It's a whole different scenario than what we are talking about here. So we are talking about people that presumably have normal neck exams, they are being seen by endocrinologists, we have already evaluated their thyroid. So it's hard for me to imagine that the numbers would change so significantly over a few years that we would end up with life threatening medullary. So the issue to me is not whether they are going to get life threatening medullary, but are they brewing some low level C-cell hyperplasia or medullary that I just can't tell from the ultrasound or from the calcitonin numbers.

DR. BURMAN: Dr. Parola.

DR. PAROLA: Just to compare exenatide and Liraglutide in pre-clinical studies; exenatide caused C-cell tumors, benign C-cell adenomas only in female rats whereas Liraglutide caused adenomas and carcinomas in both species; adenomas in all sexes and carcinomas in both sexes of rats at low multiples of clinical exposure.

DR. BURMAN: Thank you.

DR. MOSES: Can I just clarify one point there Dr. Burman? That is that those were, as I think was already presented, rather short-term studies in the animals.

DR. BURMAN: Dr. Moses

DR. MOSES: I am talking about the carcinogenistic studies for exenatide and Liraglutide.

DR. MOSES: The ones done by their Sponsor?

DR. PAROLA: They were the only ones we have.

DR. MOSES: Yes and those were with once daily administration for short overall exposure.

DR. PAROLA: I don't remember the specifics, if that was once daily or not.

DR. BURMAN: Yes. The FDA?

DR. MAHONEY: Just one comment which is that this is a new scenario, the idea of a drug induced medullary thyroid carcinoma and I am not sure that we know for sure that natural history of it would have the same indolence. I mean we don't know.

DR. TUTTLE: Although to be fair, we know it hasn't developed in a year right? I mean, there have been a lot of patients on the drug for a year so I can't rule out that it wouldn't happen in two or three or four years, but it's not happening to 50% in six months.

DR. KILLION: Right, but if you recall the slide that Dr. Parola had where he showed the latency period in the rodent carcinogenecity studies, they had to get through about 20 or 25% of their lifetime before any of them developed the tumor.

DR. TUTTLE: Absolutely. I agree. The point is, it's not sudden, it's not rapid in a year. Can we say anything about five years or ten years or 20 on the biologic behavior? I think your point is well taken.

DR. KILLION: Right. The initiation of it probably is in the indolent but the course of it, once it appears we don't know.

DR. BURMAN: Any other comments before we move onto the next question. Obviously this is extremely controversial question and we are really faced with a difficult and unsettling decision that must be based on adequate long-term data really trying to balance the efficacy of the medication versus the possible long-term adverse effect.

To summarize the discussion of this point before we go to the next one, I think there is evidence that rodent studies clearly show that the agent is associated with tumors in two species and that's unusual whether that information is applicable to humans and relevant to humans is unknown, the mechanism by which Liraglutide causes elevated calcitonin in humans is not completely understood. About 2% of people who took Liraglutide had an elevated calcitonin that was significantly elevated above the normal range whereas statistically the level went up on a medium basis for all patients. However, the levels that it rose to were very small, lower than the levels that we are talking about here that are clinically significant in a vast majority of patients. There was one patient who had medullary thyroid cancer in the group and it's unknown how many others had C-cell hyperplasia but those that were operated on for elevated calcitonins, the majority of them had C-cell hyperplasia.

As the committee pointed out, it's important for us to balance the efficacy of the agent versus the potential risk which is difficult because we are not certain of the long-term risk of the medication. It's also difficult to know what should be the pre- or post-marketing studies. Some have suggested measuring a periodic calcitonin over time and not treating patients if the calcitonin level was over a certain level. Some of us

suggested that medullary carcinoma, when it progresses from C-cell hyperplasia from medullary thyroid cancer, is an indolent processes in the vast majority of cases, it would be picked up with elevating and increasing calcitonin levels. It is still difficult to know in the post-marketing or pre-marketing studies what else should be measured. Should we measure sonograms, procalcitonin, sonograms?

Palpation would miss many significant percentages of nodules. We haven't discussed here the fact that Liraglutide seemed to increase the risk of nodules and goiter in the presentation but we can spend more time on that later, but I think we are faced with a lot of unknown issues regarding the long-term safety versus the efficacy. Are there any comments or disagreements with that or additions? All right, then we will move to the last question, we want to end around 340.

(No response.)

We're really faced with a difficult

Any comments

(No response)

DR. TU LE THI: Coming to the 2.2% who goes above upper normal range?

DR. BURMAN: Please

DR. TU LE THI: Okay, my name is Tu from statistics. I tried to look into the subjects who go above upper normal range and I looked into the two trials where you have longer exposure and I looked into first, how many of these subjects continued to be above upper normal range? and actually 47% of these subjects were below upper normal range when they left the trial and 63 of the subjects were below upper normal range at

some time point after they were above upper normal range. The highest calcitonian value at the end of the trial for these subjects were 40 nanograms per liter

DR. BURMAN: Thank you. All right. Then – then we will now go onto, for the last 30 minutes or so, 20 minutes before we go onto the question.

'Please comment on the numerical imbalance of reports of papillary thyroid carcinoma and clinical trials'. I have my views on that, does anyone want to also comment?

DR. TUTTLE: Yeah, I don't really put much weight into that at all, there was such heavy selection by us, you were picking people that had nodules, you were picking people who had elevated calcitonin, and you were finding micro-papillary which is incredibly common in the adult population. So I don't know beyond random chance in six people, four ended up in one and one ended up in another. That looked to me like not a surprising finding. When you are picking people that have thyroid disease to go to surgery.

DR. BURMAN: My comments on that are as follows. There were six cases of Liraglutide associated papillary thyroid carcinoma and one in the comparator. The rates were 1.8 versus 0.9 per 1000 patient-years, respectively. All papillary thyroid cancers were less than 9 millimeters and most had associated elevated serum calcitonin levels. In the normal populations, females have about an incident rate of 18 per 100,000 of papillary cancer and then about six per 100,000. So this is a slightly higher, a higher rate than that. Exenatide has now had nine cases of papillary thyroid carcinoma and post-marketing studies.

There was also noted a 9 to 11% likelihood of new thyroid nodules and it seems to me that the risk of finding papillary thyroid carcinoma is related primarily to the

performance of thyroid surgery and I am not sure the actual incidence is markedly elevated. Further studies are necessary. The issue of formation of new nodules is disturbing, and requires further analysis. Anybody have any additional comments on that?

DR. MOSES: Dr. Burman may I be allowed, a very brief comment or is it? Not about that specific issue.

DR. BURMAN: One quick comment

DR. MOSES: No, it's the fact that you had cited medullary carcinoma in Liraglutide treated individuals. It is actually in the comparator group that there was the medullary carcinoma. Okay.

DR. BURMAN: Thank you. That was the medullary cancer in situ.

DR. MOSES: It was one of each in each of the two groups and the one in the Liraglutide treated group had an elevated baseline calcitonin level, the one in the comparator group did not.

DR. BURMAN: Thank you. Any other questions?

(No response.)

With regard to the papillary cancer

Any comments?

(No response.)

DR. BURMAN: Thank you. Any other questions? So this is much quicker than I thought. Then with regard to the papillary cancer I think the summary is obvious. Dr. Tuttle and I and, by silence, the rest of the committee thinks that it's likely that the papillary cancer is related to ascertainment bias and the risk of that seems relatively low and there doesn't seem to be a pathophysiologic or oncogenic basis for

developing papillary thyroid carcinoma in this agent. Any comments? All right. Then, we are right on schedule and now we are going to go back to the voting questions.

DR. KONSTAM: Ken, can I just make one comment about that?

DR. BURMAN: Sure.

DR. KONSTAM: You know, I agree with everything you said. The one thing though, for my money, I would say that surveillance is necessary to be sure. I mean, there is an imbalance. I am not very concerned about it for all the reasons you said, but not to the point where I wouldn't ignore it, that I would ignore it in post-marketing surveillance. I think there's uncertainty there.

DR. BURMAN: I agree and I mentioned that, but I will expand on that. Post-marketing or pre-marketing surveillance should continue with, again it's hard to know exactly what should be done. Should it be palpation of the neck, sonograms, serum thyroglobulin levels, but something that's reasonable to help determine the exact frequency of papillary thyroid carcinoma in that group.

VOTING QUESTIONS

The questions we are going to take, we going to go to the cardiovascular questions first and we will discuss them. Before we do that, from yesterday everybody knows how to vote, anybody need a further analysis of that? Mike does. For Mike's benefit I will expand a little bit. Seriously, we have 20 seconds to vote and you don't see how everybody else is voting until the number comes up at the end and then we want you to explain your vote. We are going to have a cardiovascular question first and then go to the thyroid questions.

Question No. 1

The cardiovascular question, which is now, I'll read it, and then we want to see if there's any further discussion of that question or clarification of that question. The question is based on the preceding discussion. 'Has the applicant provided appropriate evidence of cardiovascular safety to conclude that Liraglutide 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 ratio, odds ratio, is less than 1.8? If the answer is 'no' to question 1, '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?' Any questions or clarifications of that question? Mike?

DR. TUTTLE: I guess the only clarifications for me, because I don't do these kind of studies. Are we asking, have they ruled out unacceptable risk in the patients that they selected for this study, based on whatever their inclusion criteria? Or are we asking, have they ruled out unacceptable risks for the whole world of diabetic patients? Sort of two separate issues. What standard are we going for?

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

DR. ROSEBRAUGH: So the way I would view this is, and you weren't here it yesterday when we kind of went over how the guidance has this two-step thing and the first step is, did they clear enough hurdles to allow marketing with the idea that they might do a study later to get a definitive answer? This is to kind of say, have they beat that hurdle?

DR. BURMAN: Dr. Levitsky.

DR. LEVITSKY: In the one that we reviewed yesterday, the 1.3 was the one that allowed you to beat the hurdle. This would require 1.8 would still require the post -

DR. ROSEBRAUGH: No, no. Yesterday 1.8 allowed marketing, 1.3 would have made it so that they didn't have to do a study later.

DR. LEVITSKY: Right, right. So we are not being asked that question because 1.3 has been moved?

DR. ROSEBRAUGH: Correct

DR. TEERLINK: If you could clarify what's the indication stating in terms of patient population group?

DR. MAHONEY: It's just type two diabetes that's being proposed for.

DR. TEERLINK: So we are being asked to vote, have they proved, have they ruled out unacceptable cardiovascular risk for all type 2 diabetics in whom this would be prescribed?

DR. MAHONEY: That is the population that the applicant proposes to have an indication for but Dr. Rosebraugh may expand on that.

DR. ROSEBRAUGH: Well, the only thing I was going to expand on is what really helps us a lot is when you explain your vote. So if you vote a certain way you can say, if I could do this I would vote different.

DR. KONSTAM: Can I make a comment? So, there's nothing you can say about a segment of the population that was not included in the study population. I think we had a similar situation yesterday and I think we discussed it in the sense of saying that, that could be reflected in the labeling. The labeling could specifically say that whatever we are saying about cardiovascular safety, it does not apply for example to

high risk cardiovascular patients because they haven't been studied. So that doesn't necessarily mean to say we've - you see what I am saying?

DR. ROSEBRAUGH: Right. You're kind of saying two different things. You are not saying two different things, but you each are asking a separate question. One of the questions was, if I interpret it correctly, would we limit things in the indication? Well the indication is just as we said. Your point is, in the study section or where we described the trials, we could say this is what was studied and we don't know how it applies to other populations; right.

DR. BURMAN: Are there any other questions or clarification? Mike?

DR PROSCHAN: Yes, it's not a question, but as I read this, it says, to conclude that Liraglutide rules out unacceptable excess cardiovascular risk. Then it says including evidence that blah-blah-blah. So, you need to have evidence that you have ruled out 1.8, but as I read it that does not necessarily, you know, you might consider unacceptable excess risk to be some other number right? I mean, if you don't believe that 1.8 rules out unacceptable risk, then it seems to me that, the way this was worded, that would allow you to vote no, even if you thought they showed it was under 1.8.

DR. PARKS: I'm assuming that you already know this. This is the exact same question that was asked yesterday.

DR. PROSCHAN: Yeah, I know but the other meeting we attended. This issue didn't come up because it wasn't close.

DR. ROSEBRAUGH: It is always a problem when people get to sleep on things and then get to reflect on them.

DR. PROSCHAN: Well, to me that's not an acceptable criterion. I mean, I would have to vote the way, what I think is acceptable. I would say ruling out 1.8 is not ruling out unacceptable excess cardiovascular risk.

DR. ROSEBRAUGH: Let me try to bring us back to the intent of the question. The intent of the question is to say we have got a guidance out there, where we will say for the first step, you should have confidence interval that the upper bound is under 1.8. We are having this meeting because this is a group that got caught in the interim before they could design things the way the guidance was set up. So we are asking did they do enough? That's what we are asking.

DR. PARKS: If I can just add, what you need to take into consideration on this goal post is whether or not the quality of the data that generated the numbers, the point estimate, the confidence interval, what issues do you have with the quality of those data? If you have no issues with it, then I am assuming I know what your vote would be, but if you have then you could certainly explain it, you could put that into the situation as to why your vote is what it is or will be.

DR. BURMAN: Dr. Savage.

DR. SAVAGE: I would just like a clarification on one thing you said if I understood correctly, you said that if we voted to approve it, they might do another study and I wasn't sure that that wasn't somewhat different from what I heard.

DR. ROSEBRAUGH: I thing you can rest assured they did not make 1.3 and we will require them to do another study.

DR. BURMAN: I would like to comment that this is more typical of the committee on these questions. Yesterday it went a little too quickly in terms of

discussion. So any other comments? Then, I think we are ready to vote and the question is on the board.

DR. TRAN: Please make your choice.

DR. BURMAN: The voting result was yes/8, no/5, and abstain/0 and we would like to go around the room. Start over here, please.

DR. KONSTAM: Isn't everybody wondering how I voted? Yeah, so I voted no and I guess the question, as it is stated, I just don't see how you get to a yes. I think that we just have to keep in mind that the arbitrary bar of 1.8 that exists in the guidance document does so in the setting of a broad population in terms of cardiovascular risk, pre-specified plans for ascertainment and analysis and adjudication of endpoints, none of which took place here. So as we said yesterday, I think the question is, are the data that we see somehow equivalent to that degree of certainty? For me, I need tighter confidence boundaries in order to try to think that maybe it does. In this case, we don't have a very high risk population which is understood, but in addition to that, I also would say that I am gravitating toward the more specific endpoints as being more meaningful, such as the custom MACE.

In this case, the population B I think is somewhat suspect because its un-blinded nature, which makes me concerned about those analyses. The upper confidence boundaries here are much closer to 1.8 than they were in the application we saw yesterday and does it appear to me to be sensitive to the analytic method? Certainly in some of the analytic methods, some of the analyses, it's certainly bought up against the 1.8 which doesn't give me any comfort. So for those reasons I really don't think it meets the spirit of the guidance document.

DR. BURMAN: Thank you.

DR. HENDERSON: Jessica Henderson, I voted no, but with a heavy heart. I just wasn't a 100% confident that the risk was ruled out.

DR. PROSCHAN: I'm Michael Proschan and I voted no as well. To me, I don't think that they have ruled out the possibility of an unacceptable excess cardiovascular risk. I am also troubled by other things like the fact that the relative risk versus placebo was greater than the relative risk versus comparators. So taking that into consideration together with the issue of adjudication and everything else, to me it didn't rule out unacceptable excess cardiovascular risk. It seems like it doesn't have it, but it doesn't rule it out.

DR. FLEGAL: Katherine Flegal. I voted yes, also with a heavy heart. I based my vote primarily on the total comparator of the population A results. The point estimates were favorable, yes the events are small and I think you can't truly rule out ever really excess risk as a challenge, but there will be further study of this question. I thought given the favorable point estimates and that it was the optimal population within the study, which is limited, I felt that a yes vote was reasonable.

DR. BURMAN: Ken Burman; I voted yes. I think the findings have to be interpreted and be consonant with the guidelines published by the FDA and I think that the total comparator guidelines were within the 1.8 upper limit. There are caveats of course; the events weren't adjudicated, there was a small number of events, the study is over a relatively short period of time. I think the same guidelines have to be applied throughout different drugs and different medications. I think their results were within 1.3 and 1.8 for the upper limit. So I do think it's very important that post- marketing very specific studies be performed.

DR. FELNER: I'm Eric Felner, I voted yes. I think similar to our previous meeting vote, this group, the Sponsor came into this after most of the studies were completed, after the new regulations were set last summer and I think they did everything they were supposed to do as best they could giving the retrospective look at the cardiovascular risk and I think this drug has great potential and even more potential if it's used early in the condition. I take care of kids with diabetes. So I would love to start treating kids early with it and seeing if we can avoid all those long-term complications, or a lot of those complications, that you end up seeing having disease that's not effectively treated for a significant period of time.

DR. TUTTLE: I'm Mike Tuttle. I voted yes. More importantly, I didn't have to sit through yesterday's meetings. I think the most important thing for me is that I don't think it's fair to change the rules once we are through. Once we change the rules we would only stop a project if it has some major, major safety issues and the question here says does it rule out unacceptable excess cardiovascular risk? I think it does in the population that was studied. It's great to have a problem that you have event rates so low, it's hard to imagine that you will see a huge difference in excess relative risks with those lower event rates. So I voted yes, I thought it was acceptable with the understanding that there would be some additional follow up evaluations.

DR. LEVITSKY: Lynne Levitsky; I voted yes, I think that the studies met the guidelines and there will need to be follow up studies, but the company did a great job of dealing with some retroactive look-sees at their data.

DR. WYNE: Kathleen Wyne; I voted no. I really again compliment the Sponsor and the Agency for all the work they've done to try to pull out any meaningful data. Unfortunately, as we have said, this development program was completed before

this issue was raised, before the guidance came out, and they just simply don't have the information to answer that question. I don't believe that my vote on this procludes the drug from becoming approved and becoming available for our patients to be used. I do feel strongly that it's important to do the post-marketing trial that they have proposed which would then answer the question about cardiovascular safety.

DR. TEERLINK: John Teerlink, I voted no. This isn't fair, but I don't think public safety and public health is fair. We need to be able to protect the public health, but I don't think we have the data here to do that adequately. I think the Sponsor and the FDA did a great job with the information they have, but we have 40 events to try to determine whether there is going to be a long-term adverse outcome of a drug that's going to be given to millions of United States citizens and throughout the world.

As I suggested at the other meeting, there are problems with low event rates, they are very, very low event numbers, in addition to non-adjusted, non-adjudicated events, but in addition to that we now have a non-consistent confidence interval and point estimates that are susceptible to which study groups we look at. Even within the one, the upper bound is nudging 1.8. Then you also have an unblinded follow up here that actually contributes most of the events. So I am a little uncomfortable with that and that's why I voted no.

DR. KILLION: I'm Rebecca Killion and I voted yes, unsurprisingly probably for some. I think that this particular drug was caught in the cross hairs of the gap period and I think that given that set of circumstances, the FDA and the Sponsor had done a great job of trying to shake the most important information out of this data. I am excited about this class of drugs for diabetics. I am concerned about the cardiovascular risk, but I am also aware that a large segment of the population that is not their primary

concern at this point and I think that the potential that this class of drug offers for younger diabetics is very encouraging. I thought that the FDA guidelines were satisfied as they were asked to be and that additional information will come out in the proposed study, post-marketing studies. So that explains my vote.

DR. SAVAGE: I'm Peter Savage. I voted yes, but with considerable reservation, because I think the design of these studies, although again no fault of the Sponsor because they were playing by the old rules was weaker than it should have been. I think that excluding people with cardiovascular disease for a diabetes drug is just not something we should accept in the future. With that said, I think there should be some restrictions on the use of these drugs until there's more certainty about whether or not it's safe in high risk cardiovascular patients. Again, if I was trying to compare where I was if 1.5 and above was no and below was yes, I was 1.45 or something. I had a lot more reservations today because I think there are things that remain uncertain, but I think there's a group of relatively low risk diabetic patients who potentially could benefit from this drug without any undue cardiovascular risk.

DR. LESAR: Timothy Lesar; I voted a troubled yes. Troubled by the low number of incidents that the population studied, certainly by the placebo comparator, but comforted somewhat by the total comparator statistics, troubled also by some of the changes, their sensitivity to evaluation method, but again comforted a little bit by the assurance to the FDA. I voted yes.

DR. BURMAN: Thank you. In summary, it seems that, to summarize the 'no' votes, they were concerned about the low event rate, the lack of adjudication and the applicability to more higher risk populations as well as the concern about the statistical

analysis, especially in the placebo group. We would like to move now to question number two which is the first thyroid question.

DR. KONSTAM: Well, I guess I didn't answer this part. What additional cardiovascular data are needed to address any limitations resulting? So did you want us to address that, I am not sure have we addressed that? I didn't try to address that in my comments. I would like to say a couple of things about it.

DR. BURMAN: Sure, if you want to say a comment.

DR. KONSTAM: Well, I mean, first of all I actually would like to say that even though I voted no on this, per the prior discussion, I would accept this degree of evidence if I am very confident that this represents a major clinical advance. I have heard from my diabetes colleagues and also from Ms. Killion that they think it might in fact represent a major clinical advance. I heard from the Agency some uncertainty about that, but I just want to go on record as saying that, to the extent that, so I don't know how to come down on that, but I would just like to say to the extent that this is a major step for diabetes care compared to what exists out there, I would be willing to accept this level of risk in approvability.

So I just want to sort of make that statement. The other thing, in terms of going forward, obviously it needs another trial to assess the risk. One question that I would ask and I'd love comments from the statisticians is whether there is a way of incorporating existing data into improving the assessment of risk as opposed to relying on a very large whole new trial and I just sort of would raise that question with trepidation. Is there an approach to it? Is there a Bayesian approach, for example, applying the favorable signal, it does exist in this data, to sort of get to an acceptable level without a huge additional trial.

DR. PROSCHAN: Well, I think there might be a Bayesian way to sort of set a bar that's different from the 1.8. I mean, I can imagine sort of Bayesian methods where you accepted if the probability that the odds ratio say is bigger than a specified number is – is lower than, you know, 20% or something, 10%, whatever you want to make it. So, I actually think it would be – in fact that's one of the options I was thinking about for trying to figure out what criteria because I am convinced that, you know, there are better ways to do it. So that's certainly an option. The problem is, it depends on how you formulate your prior information and if your prior information is sort of neutral then that might be acceptable. You can end up making it too easy to pass. So, you know, I think that's worth investigating certainly

DR. BURMAN: Okay, thank you both. Let's move onto the first thyroid question which is on the board. We will open the question for any specific clarification.

Question No. 3

Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans?

a. If voting "Yes," why?

b. If voting "No," please explain why not and provide recommendations for clinical trial monitoring for thyroid C-cell tumors in the development programs for other GLP-1 analogs. Any points of clarification or comments on that question? No? All right, Paul you are ready? Okay, then I think we are ready to vote

DR. BURMAN: The vote was 1/yes and 12/no with 0/abstains and we would like to go around the room perhaps now starting on this side.

DR. LESAR: Timothy Lesar, I voted no. If I read the question literally that, I think these animal findings are troubling and I believe there's not enough human

data to suggest that they are not important, I was not totally convinced by the mechanistic explanation that was used.

DR. SAVAGE: Peter Savage. I voted no. I felt that the animal data was worrisome and I didn't see sufficient human data to feel reassured. I also am not convinced that the benefit of adding this drug with this unknown risk at the present time outweighs the tradeoffs, probably not so much in terms of metastatic cancer, but the extra burden on patients, unnecessary surgery and all these things that came up in the discussion. It's a fairly, you know, it's a significant cost for patients and if you give this drug to millions of people it's actually going to impact a fair number of people. So, even if the screening is relatively low level, so I think that some of these other questions need to be better answered.

DR. KILLION: I am Rebecca Killion. I voted no, no with an explanation. This is one of those situations whether yes and no are very unforgiving. So, I didn't think I would ever be quoting Donald Rumsfeld but, I feel like there are no "knowns" and there are the unknown, the known unknowns and then there are the unknown unknowns and I think that's sort of the territory that we find ourselves in right now is that we just don't know. At least I certainly was not clear, but I have hope that with further study we will be able to get some comfort on this level and so I am sure that, that will be investigated. So that's my no with a very hopeful explanation.

DR. TEERLINK: John Teerlink. I voted no, largely for those reasons but I won't quite Rumsfeld. The other thing, I am not convinced that what we know about human carcinomas actually translates the drug induced kind that we are seeing here, I don't know yet. I think I need to be a little more convinced about whether, what we think

we know about the natural history of these carcinomas in humans, translates to what we think may or may not apply to potential drug induced.

DR. WYNE: Kathleen Wyne. I voted yes. I really took this question as a literal scientific question and from a scientific perspective the data they showed me with respect to things like receptor binding and so on, I just felt that it did not suggest that we were going to see the same effect in humans C-cells as we see in the rodent C-cells. Now, the associated issues of monitoring and what we don't know about the natural biology of these cells, as I said I took this as a literal scientific question and all the peripheral issues I felt went into the later on questions.

DR. LEVITSKY: Lynne Levistsky. I voted no and I must say that my major concern was related to the younger end of the age group, which is that the people over 18 who would be as eligible to get this as the people who are 55 or 60 who have a very long life span ahead of them, might respond very well to this drug for much longer and I think that there's enough concern about the rodent data, although the data in humans so far really don't support that we are going to find anything that that particular population will require some monitoring just because of the length of exposure that they might have.

DR. TUTTLE: Mike Tuttle, I also voted no. I don't think the data that we have allows us to comfortably rule out that there might be an effect in humans and that probably should be the bar we would set with this kind of pre-clinical data. So no, I think I wouldn't be surprised at all over the years if people are exposed to this drug for years and years and years, if they developed a little C-cell hyperplasia and maybe even medullary cancer years down the road, that wouldn't be terribly surprising. I think when you look at the risks versus the benefit of this drug, the risk is not just the risk of

developing C-cell hyperplasia, but it's the risk of, if you are going to go on this drug getting that screening calcitonin, getting the screening ultrasound, and the risk of surgery. So as we think about approval and marketing stuff that the risk of unnecessary surgery screening has to sort of go into this as well.

That doesn't mean from an individual patient I don't think they should necessarily not be given that option, but it's something that needs to be explained to them. So in terms of the monitoring for it, as much as I dislike it, if I was going to use this drug, I'd do a screening calcitonin, I'd do a screening ultrasound and I would follow those once a year for a bit. That will detect a lot of false positivity and that may decide whether or not you want to proceed on with it. Based on the animal data I would be uncomfortable following a patient without a calcitonin and ultrasound, based on what we've seen.

DR. FELNER: Eric Felner, I voted no also. I think just with all of the discussion, I think Dr. Burman actually said it best directly related to this question, which he said was unanswerable. Commenting from the discussion that was going on and to answer the question the way it is literally written, would be no. However if you change the word and said to demonstrate these findings *are* relevant, could give the opposite answer and be more in favor of it.

I think as far as screening goes, in pediatrics it's very simple for us for medullary carcinoma of the thyroid, we get a child in that the parents or somebody in the family has the disease, the first thing at least that we generally order is a RET proto-oncogene and if it's negative we get a calcitonin with it, but we are very comfortable. So I don't know if looking at trends of calcitonin in those that really exceed a level that would be concerning, then looking at the RET, although that is not the most cost effective

way, but that would be another tool that may be helpful since that seems to be the bigger player here in these patients that develop medullary carcinoma of the thyroid.

DR. BURMAN: Thank you. Ken Burman, I voted no. My summary is, the issue of calcitonin elevations in human and C-cell hyperplasia and adenomas and cancers that we found in rodents is unsettling. The calcitonin is a marker for medullary thyroid cancer, but mild elevations can be non-specific and can occur with other medications and other conditions. The seminal question is whether increased serum calcitonin levels are a harbinger of C-cell hyperplasia and ultimately medullary thyroid cancer in RET negative individuals? It is impossible to know at present the answer to that question. The progression from hyperplasia to cancer does in fact occur in RET positive individuals and it is not known with certainty whether that occurs in RET negative individuals.

The human clinical studies do not adequately address the question of elevated calcitonin due to small numbers of cases and relatively short follow up. It is also worthy of note that elevated serum calcitonin concentrations can occur in other disorders such as neuroendocrine small cell tumors and there's no information regarding those sites. The presence of Liraglutide used in selected populations should be commented on, such as RET positive subjects and goitrous subjects, since the effect is unknown. It is likely that the mild calcitonin elevations are non-specific and not a harbinger of malignancy, but without further studies we cannot be sure. We are faced with virtually a modified Hobson's choice with a difficult decision that must be based on inadequate long-term data. I think our goal is to err on the side of caution regarding possible adverse events for the population even if the drug may be efficacious, especially in this clinical context.

DR. FLEGAL: Katherine Flegal. I voted no. I feel that we can't comfortably rule out some relevance to humans with the two species and the two genders. We really can't ignore that data. There's also increased risk of unnecessary screening although that appears to be a risk whether or not the drug actually increases the risk of medullary thyroid carcinoma, but I felt in the context we really just couldn't be sure.

DR. PROSCHAN: I am Michael Proschan and I also voted no for the same reason basically that I just don't know how you could really be comfortable in knowing that it's not relevant to humans.

DR. HENDERSON: Jessica Henderson, I voted no for the simple reason you just can't dismiss the data from the rodents.

DR. KONSTAM: Mark Konstam, I voted no. You know, we are in unchartered territory with regard to a pre-clinical signal and without any associated clinical evidence in previously seen similar signals. So it's really unknown and even if the Sponsor and the Agency had agreed on the mechanistic hypothesis, it still wouldn't have assured me that this is not clinically relevant.

DR. BURMAN: Dr. Joffe.

DR. JOFFE: I just wanted to let the 'no' voters note that we asked the specific second question for that question specifically to provide recommendations for clinical trial monitoring for thyroid C-cell tumors in the development programs for the GLP-1 analogs. As you have already heard, some investigational GLP-1 analogs and agonists have also these similar types of non-clinical findings. So we are in a quandry for how best to monitor those in the clinical trials. Novo noticed that calcitonin simulation testing, which we didn't spend too much time talking about, but I would like to hear at least some thought whether that is useful to continue to do or not.

DR. BURMAN: Hylton, thank you for bringing that up. Would you mind if we discuss that after the second question which is more relevant for a clinical disease?

DR. JOFFE: Sure.

DR. BURMAN: To summarize the 'no' votes, the issue really revolves around how applicable the rodent data is to humans and that obviously the panel is worried and concerned that finding carcinogenesis and neogenesis in several species potentially a worrisome sign, there were a low likelihood of events in the human studies. The question here really relates to the possible applicability to humans and the elevated calcitonins that were found. We'll have more to say about that in the next question.

Let's move to the second question, which is, 'Assuming the remainder of the risk/benefit data are acceptable, do the available data on thyroid C-cell tumors permit marketing of Liraglutide?'

a. If voting "Yes," explain why? Please comment on the need for and approach to post-approval risk management (e.g., whether baseline assessment and/or ongoing monitoring for medullary thyroid cancer is needed for Liraglutide-treated patients. If so, what types of assessments should be done?).

b. If voting "No," why not? What additional data related to medullary thyroid cancer are needed to support marketing?

Any specific clarifications by the committee on that?

(No response.)

So it really is the critical question, do the available data on thyroid C-cell tumors permit marketing of Liraglutide? Any questions?

(No response.)

DR. TRAN: Select your vote.

DR. BURMAN: The vote is a virtual tie. 6/yes, 6/no and 1/abstain. I think reflecting the difficulties and the issues. I think we will start with Marvin to explain.

DR. KONSTAM: Yeah I'll be happy to explain my abstention. You know, I have always wanted to abstain and I could think of no better question for a cardiologist to abstain on, but now that I realize I could have been a tie breaker I might re-think it.

DR. BURMAN: Marv, do you have any other comments on why you had such a hard time?

DR. KONSTAM: I have listened to what you have all said and I don't come away with a clear opinion about what to do here, in terms of going forward and monitoring. I really would leave that to people with some expertise in the field.

DR. HENDERSON: Jessica Henderson; I voted yes. In all the discussion we had previous, the comment that stuck me the most was by Rebecca Killion, that this is a manageable risk, not a sudden onset risk, and so that was the main reason I voted yes.

DR. PROSCHAN: I'm Michael Proschan. I voted no, but I don't – this question I am not sure because I don't know, whether some sort of labeling might be sufficient, maybe you could say, well it's sufficient as long as you have appropriate labeling. So it's a wishy-washy no, really.

DR. FLEGAL: Katherine Flegal. I also voted no, probably also kind of a wishy-washy no. I guess this question includes assumptions that the remainder of the risk benefit data are acceptable and I think you have to look at this in this context as well. It seems to me, in our current state of knowledge that this exposes people to potential

excess risk. We don't know if this drug induces these kind of cancers. Are there going to be as indolent as the naturally occurring ones? There are other risks of continued monitoring, excess thyroidectomies and so on. So I voted no, but it's a very difficult question.

DR. BURMAN: Thank you. Ken Burman; I voted no and obviously a difficult decision, as I had mentioned earlier, weighing the benefits versus the potential adverse effects. I do think it's an optimistic no and the optimistic no is related to the fact that I think we need more information that can be obtained in the post-marketing studies or the pre-marketing studies as the case may be, but to answer Hylton's question from before, there are many ways to design them, but their clinical studies should periodic calcitonin levels, pro calcitonin levels, I believe, CEA levels on a periodic basis, periodic sonograms, and perhaps calcium stimulation test, although I personally think they are less sensitive in the patients who are treated with the agent to prove over a longer period of time that the C-cell elevations in the serum are transient and non significant. Then I will grant you that part of the dilemma is that the elevations were very minimal and are not generally considered clinically significant in the vast majority of the patients. They were significant in a few patients

DR. FELNER: Eric Felner; I voted yes. Again, I think that the benefits of this medication have an excellent opportunity, especially earlier onset in the disease, but the screening, as I mentioned before, family history, calcitonin trends, and possibly the RET proto-oncogene, but I would hate for us to miss out on this new medication that seems to have excellent benefit profile with really not, at least well described, we are all questioning this first question that most of us voted no on and then I would hate to miss out on getting this medication in the blood.

DR. TUTTLE: Mike Tuttle. I voted yes primarily because I can't think of two more years worth of data I can send the Sponsor back to that's going to make me happy. You can work on mechanism action, that still going to tell me whether it will cause a tumor in 20 or 30 years. You can do it in 9000 people for two years and I am going to be sitting here two years from now asking you the same question. So I just don't see how the new class of drugs like this doing more and more sort of research studies is going to get me at the answer that I need to know. I suspect unfortunately the only way we are going to know this answer is to expose a large part of the population for ten or 15 years and that's probably where we will really find out whether we see some C-cell hyperplasia.

I am impressed with the one and two year data that it doesn't look like it's causing tremendous problems early on and I think with appropriate explanation to my patients understanding the risks and benefits, many of them would think that the benefits of this drug outweigh the risk, but it would just have to be as unknown. I am not a huge fan of the calcium stimulation testing. It's a poor step-child of the calcium pentagastrin stimulation testing. Its sensitivity is not as good, it's also not a lot of fun for patients. It's not a fun test to go through. So I would probably design it in a subset, but I certainly wouldn't recommend it for everybody across the board, maybe a subset of patients that we figured out had a little higher risk of developing it or just a random subset. I think it probably wouldn't add enough to put every patient on future studies through this stimulation test.

DR. LEVITSKY: Lynne Levitsky; I voted yes and as I was thinking about it, I was thinking that in the age range I would be dealing with thyroid carcinomas occur, but they are not all that common. Medullary thyroid carcinomas make up about 5% of

that population. That means that you would have to have a very large study to find it, so the surveillance issue becomes important, you would really have to survey a large population. If you are going to do that, as I was thinking about it clinically, I think I would only want to do only one test, it would just get complicated to do more than that. I probably want to do a calcitonin and then I would want to do some of the other tests that were suggested by Dr. Burman if the calcitonin came up a little bit elevated and yes, there would be this opportunity to get caught in the vicious cycle of elevations of things and needle aspiration biopsies and surgery on more patients.

I think the only way to see this through is to, as was just suggested by Dr. Tuttle, expose a large population to make sure that this really is not going to be an important event, because if it doubles or triples the prevalence or the incidence of medullary carcinoma of the thyroid, one is not going to find it out except by this sort of large scale surveillance and if it does anything I would guess that that's all that would do.

DR. WYNE: I'm Kathleen Wyne. I voted yes. With respect to the issue of what is happening with the C-cells, I share everybody's concern about the rodent data. However, as we look at the human data, as someone said, it's not only that it's a very low level in a small signal, but there's some data there, we have a process that has a manageable risk and we have had several people propose to us ways that we can manage and monitor it. So we do have a screening test, we have a test that has a reasonable sensitivity and specificity that we can do safely in our patients.

I don't know exactly the cost, but it is something that we can do easily. Some may have to go onto the Pentagastrin stimulation test, which is quite unpleasant and we will certainly try to avoid that if we possibly can. That's right, because you can't get Pentagastrin anymore, we have to send them to Europe if we want to do Pentagastrin,

by the way. Still, doing the calcitonin, maybe the procalcitonin in some patients, again as they mentioned the physical exam and actually the ultrasound are somewhat insensitive because a lot of our patients will have multi-nodular goiters and we only biopsy the dominant nodule which is not going to have a micro C-cell hyperplasia in it.

We do have a pretty sensitive marker, which is our blood markers, and it is something that we can follow in the patients. We just simply don't know how often we are going to need to do it, but as it was said, I think it is a manageable risk. Also we know that there's going to be a very large trial coming, which can generate more data for us on this subject. So that adds to me the comfort that as we look at it long-term, we are going to have data coming into the long-term risk. So I think it's important to not prevent patients who need a therapy that's beneficial and that they may be more compliant and adherent to we should not prevent it from becoming available to them as long as with have this manageable risk.

DR. TEERLINK: John Teerlink and I voted no, though I was tempted to take Dr. Konstam's route out and abstain. Had this only been about the natural history of thyroid cancers, I probably would have been more tempted to do that, but I think it's impossible to extract or separate the process by which these patients will be screened and the potential collateral damage from that screening and all the related surgeries and other things that may be related to that from the issue of the actual thyroid cancer occurrences and the natural history and all those things that we just don't know anything about.

The combination of those things made me more uncomfortable and vote the way I did. I would note to the Sponsor, this is actually an opportunity to get your chance to say, well, we can actually get a very good definition on what the benefit risk is and provide to the investigators of this future trial, a real pathway saying follow this and

if you follow this, we may have not only will we not discover hopefully any thyroid cancer, but hopefully we will be able to say we really didn't cause much risk in the screening process that we put into place.

I would really encourage you to go ahead with that. In terms of recommendations on how to screen, I clearly defer to my endocrinology colleagues. Please take a look at that total risk benefit and try to provide some, because a couple recurrent laryngeal nerve damage, a little MRSA infection in the neck, etc, etc, by the time you start adding those up, the control of blood glucose may not be balanced by all those other events.

DR. KILLION: Rebecca Killion; I voted yes. I feel like my voting today is causing me to be at risk of whiplash. It's very difficult to seesaw between these things because there are clearly arguments on both sides, there are concerns on both sides, but I think that again we are in that area of the known unknown, we know we don't know. Socrates said that's a wise man who knows that he doesn't know. I think there are work-arounds here and I trust that someone else is going to figure out what those are, but my overall sense is that risks were manageable and that the risk management decisions here probably shift to the patient and the doctor, which is probably where they ought to be in cases like this anyway. So, you know, even though I was a bit conflicted I am pretty comfortable with my yes vote.

DR. SAVAGE: Peter Savage; I voted no. I just don't think we have enough data to be reasonably confident of the safety in humans for long-term use and, you know, it's been mentioned that they could, this drug or this class of drugs could be particularly useful in young diabetic patients, but those would be the patients who would be most likely to have a serious consequence if they were on one of these drugs for a

longer period of time. So the other issue I had, as I mentioned before, is that I don't think it's the only way to get blood sugar under pretty good control. I think there are – there's a whole armamentarium of drugs out there now and I am not sure that it's, I haven't heard enough about the unique advantages of adding this drug to feel confident that the potential disadvantages although the actual risk of cancer may be relatively low, the greatest risk may be being entered into the American medical care stream being screened for this sort of thing and that's something that would be out of our control, once it was out on the market.

I think it also should be made clear what is the benefit of this drug or any of the others in the class that have a longer duration of action over the existing drug that's on the market? I know that there's fewer injections and so forth, but what the other benefits should be, it should be made clear, and it certainly sounded from what I heard today that this may be a class effect for any of the longer acting agents and I would also urge people to go back and look at the existing any sort of population data that you could get on patients that have been taking exenatide to see if there was any information, I mean negative information would be useful and positive information would be useful because there are a substantial number of patients who have now been treated for longer than the period of time in this study

DR. LESAR: Timothy Lesar; I voted no. I tried to talk myself into voting yes, but I couldn't. I do not believe the data very strongly supports that there's a high risk to this drug, I think it was the unknown part that bothered me the most. I believe there wouldn't be a whole lot of data that would require me to switch my vote, but I think I am just too unsure. It also it has to do with the recommendations, how would we follow these people? I think in the real world situation I was very concerned like others

are, about what risks we pose to patients, they assign what the monitoring that people might do to monitor for the thyroid effects of this drug. I also believe that this class including short agents should be further evaluated for potential risk or lack there of and so that in the perfect world I think I probably would have voted yes, but since it's not that I had to go with no and so that I am balanced. I believe that the risk to patients at that current time is greater than the potential benefits.

DR. BURMAN: Thank you all. To summarize if I might the yes votes, the people who voted yes thought that the risk was slight for C-cell hyperplasia and medullary cancer in humans.

DR. BURMAN: Those who voted no were concerned about the unknown effects of the agent on C-cells over a long period of time given the small number of patient study thus far, that there are alternative agents available and that they were worried as well about so called collateral effects of increased costs to the healthcare system and potential risks to patients who required screening and then had a subsequent thyroidectomy or other procedure. These are difficult to assess and to quantitate but in essence, the people who voted no didn't want to expose the entire population to a possible risk that was still undefined and indefinable and there is the question of the effect on other tumors.

However the post marketing studies, and I would say in my personal view from the assessing the conversation and the voting is that it seems that even the people who voted no were very close to the margin of going over the border and voting yes and that further studies such as post marketing studies that have been suggested or recommended, Dr. Tuttle has noted that these studies might take a long time, but on the other hand, it's possible that if the calcitonin went up for the short time and then went

down are that there was no clear indication over a short period of time meaning 6-12 months that those pre or post marketing studies might help abrogate our worry regarding the potential possibility of carcinogenesis or C-cell hyperplasia. We have one more question to vote on, Dr. Levitsky.

DR. LEVITSKY: I was interested to hear the last comment because one of the things this did for me is make me worry about Exenatide a little bit. I mean the way we are using it, we are turning it into a long acting drug, and I am not convinced that the same worries don't reside there. I mean they are pretty small worries but I am not worried about finding something in 6-12 months. I am worried about a long-term use, which will then pop up some cancers, not some C-cell hyperplasia and I don't think we can be sure about that with any of the agents in this class, whether long-term or short-term, that's troubling me now actually.

DR. BURMAN: It troubles all of us, seriously.

All right, let's move now to the last question, the last voting question, which is on the board.

Question No. 3

Assuming the remainder of the risk/benefit data are acceptable, do the available data on papillary thyroid cancer permit marketing of Liraglutide?

a. If voting "Yes," explain why? Please comment on the need for and approach to post-approval risk management (e.g., whether baseline assessment and/or ongoing monitoring for papillary thyroid carcinoma is needed for Liraglutide-treated patients. If so, what type of assessments should be performed?

b. If voting "No," why not? What additional data related to the papillary thyroid cancer are needed to support marketing?

So the floor is open for clarifications of this question regarding papillary thyroid cancer.

(No response.)

Seeing none, then we will move onto the question, which is on the board. Assuming the remainder of the risk/benefit data are acceptable, do the available data on papillary thyroid carcinoma permit marketing of Liraglutide?"

DR. TRAN: Please select your vote.

DR. BURMAN: The vote is, for the record, 12 yes, no zero, abstain one. I think, oh I am sorry; we will start on this side, yes.

DR. LESAR: Timothy Lesar; I obviously voted yes. Again it would have to do with the discussion that occurred at - in the small difference in rate based on what the population frequency appears to be and I was not convinced there was a risk.

DR. SAVAGE: Peter Savage; I voted yes essentially for the same reasons as have just been said. It sounded from the discussion that the risk was acceptable.

DR. KILLION: Rebecca Killian; I voted yes, same reasons.

DR. TEERLINK: John Teerlink, yes, as above, see below.

DR. WYNE: Kathleen Wyne; I voted yes. I think the summary earlier said it best that it appeared to be an ascertainment by us. So it's - I felt that it was okay to vote yes.

DR. LEVITSKY: Lynne Levitsky; for the same reasons that everyone else has had.

DR. TUTTLE: Mike Tuttle; I voted yes for essentially the same reason and because the follow-up program for detecting papillary thyroid carcinoma is feeling the neck and doing thyroid ultrasounds anyway. So if we are wrong and there is a

papillary signal, we will find it while we are looking for the C-cell hyperplasia and medullary.

DR. FELNER: Eric Felner; I voted yes for the same reasons that have been discussed.

DR. BURMAN: Ken Burman; I voted yes. I think the risk is low and there is mainly ascertainment bias as I had mentioned earlier.

DR. FLEGAL: Katherine Flegal; I voted yes for the same reasons everybody else has given basically.

DR. PROSCHAN: Michael Proschan; and I abstained partly because I thought that was really brilliant of Mark to do that because if you vote yes or no, you have to explain your answer, if you abstain, it doesn't say why did you abstain. I don't - I can't really tell whether there is a real problem or not and so I - that's why I abstained.

DR. HENDERSON: Jessica Henderson; I voted yes for the reasons given previously.

DR. KONSTAM: Well, you know, Dr. Daniels over there actually taught me everything I know about the thyroid, he doesn't - probably doesn't remember but when I was a house officer in Mass General and the only thing I remember is that a papillary carcinoma is much less mysterious than medullary carcinoma. That seems to be born out by the discussion here. You know, the signal here is very small, I do think that this requires post marketing surveillance.

DR. BURMAN: This is an easy one to summarize. The vote is unanimously yes for the reasons that were obvious and I will just mention briefly that the risk is low; it seems to be as ascertainment bias and it doesn't seem to be a real signal as long as there are further follow-up and post marketing studies.

Does the FDA have any other comments or questions or issues they would like to bring up this afternoon?

DR. PARKS: We're looking at the question. We are not entirely sure if you have given some sort of clarification to why you voted in a certain way. So just one more moment please.

DR. BURMAN: Sure.

DR. PARKS: I think this really goes to, for the second question on medullary thyroid carcinoma, for those who voted no. It's not clear to us what it is that the applicant would need to do to address that, I guess you would call it a pre-marketing study.

DR. BURMAN: Well, could you put up the list of the people who voted no?

DR. TRAN: Yes.

DR. BURMAN: Is that right - that.

DR. PARKS: It's the one where Dr. Konstam abstained. That's the only way I can remember it.

MAN: That's known as a biomarker.

DR. BURMAN: That's the first one - the first question Dr. Parks.

DR. TRAN: Yeah, that's the one.

DR. BURMAN: Okay regarding the medullary cancer.

DR. TRAN: Number two. Right there.

DR. BURMAN: Okay, should we just go in alphabetical order. I'll start with a no explanation. As I mentioned, the reason I voted no to the question, which is

does the available data on thyroid C-cell tumors permit marketing, I think that there is, it's unknown whether C-cell hyperplasia, yes.

DR. PARKS: I'm sorry. Actually what we need is the second explanation, what additional data related to measure thyroid are needed to support marketing.

DR. BURMAN: Thank you. Yes, my opinion is and we will go around the table is that we don't need much and I think it's partly an unanswerable question because you have to wait a long time many years or decades possibly if there is really C-cell hyperplasia evolving into medullary thyroid cancer. I would feel assuaged if there was a 6-12 month study, extension study looking at Liraglutide and documenting the calcitonin levels to ensure they don't continually rise, I would feel good if they stayed the same and if many of the dropped as was indicated earlier, I would feel good about that.

I would feel better as well if they measured other markers such as medullary cancer, which was CEA and pro-calcitonin and I would feel fine if they had an occasional sonogram of the neck to just document that this mild and I would emphasize very mild elevation of calcitonin is clinically insignificant and isn't a harbinger of worse prognosis and medullary thyroid cancer. I realize no study of a short duration, meaning several years, is going to answer the question definitively but I think I would be assuaged with the information over a period of 6-12 months. I would like, with your permission, the opinion of everybody else who voted no. Dr. Flegal.

DR. FLEGAL: Well, I really don't have much to add to add about it. I think we need a little bit of a closer look and I would like to see if the calcitonin levels continue to rise or if they rise and fall and have just some additional information that

looks at this question a little more closely. So I would also feel better with a little bit closer look.

DR. BURMAN: Dr. Lesar.

DR. LESAR: I too would agree that some earlier short-term trial data would be comforting. As I said, I was not very far from voting yes. I think the issue related to biologic measurement should be put into context that it will not result in an excessive cost and then needed measurement in monitoring patients who might end up on the drug. Also, I would like to see what the realms would look like and that didn't place patients, that increased - substantially increased costs and risks and so that it's balanced.

DR. BURMAN: Dr. Savage.

DR. SAVAGE: I think some data maybe a little bit longer period of time, maybe two years or something to indicate the - to make sure that we are satisfied that this isn't going to change in a negative direction. I also would suggest looking at longer term followup on the drug that has been in use just to make sure there isn't either some signal we haven't heard about or to have the reassurance because I agree with the comment that was made that maybe there is something else going on that we just haven't noticed because this is a rare condition. So I think some type of a surveillance of maybe electronic databases from some organizations that have the ability to link together where there is someone on Exenatide has been diagnosed with thyroid carcinoma.

DR. BURMAN: Dr. Teerlink.

DR. TEERLINK: As I tried to say before, I think it's really important to get a sense of, since I think the screening program is going to be part of this drug that has in and of itself risks and benefits. I think it's very important to say in the context of this

what are the risks and benefits that are being added to the drug, which protects, itself from the screening program.

So you need to see how many drive-by thyroidectomies are being done because we are going to have - you are going to have this drug, which is going to have a label saying, this might possibly, in animals, it might cause two thyroid cancers in two types of animals and people are going to say unfortunately, I think in the US healthcare system, safer to look and oops, I found something there, okay, well it is safer to just take the thyroid out. I am concerned about how often that might or might not happen. In addition, I am also not convinced that we truly understand the biology of drug induced medullary carcinoma; I don't know so.

DR. BURMAN: Dr. Proschan.

MR PROSCHAN: Well, given that these cancers are going to take many years to develop and so you wouldn't see them in a trial of a few years, I would have to defer to the expert, namely you, on what would be an acceptable trend in these other markers.

DR. BURMAN: I would emphasize that all of us, speaking for myself, who voted no were very close to saying yes. It's an optimistic no that we just need, in my opinion, a little longer data and nothing is going to answer the question short of many decades. The question, the crux of this issue is should we expose the entire population to the potential risks albeit, likely to be low and potential collateral damage of thyroidectomies etcetera and costs if we can get a little extra data to show that we have a little better feeling about the low risk of elevated calcitonins and especially if they trended back down toward normal.

Does anybody want to comment? Marvin.

DR. KONSTAM: Yes, so what I would say to the Agency is to really go back and take the comments of our diabetologists to the effect that this really represents a substantial increment in clinical management of diabetes. Go back and really look at the superiority data and the information on hypoglycemia and see - because I don't think we really heard a really good analysis of whether or not the data really support that view, because if it is, I mean, if you come away from this with those comments in the data that this really in your view does actually represent a major clinical advance then I would go ahead and approve the agent with a black box warning and whatever screening you can get from your thyroid experts.

If you don't do that, if you can't do that then I would not recommend approving the drug. How would I get there, well, if it's not a major clinical advance then I think you need enough clinical data to indicate to you that you really don't have a human problem. Otherwise I wouldn't approve the drug.

DR. BURMAN: Dr. Tuttle, you had a comment?

DR. TUTTLE: You can get at the issue of this drive-by thyroidectomy thing. The Institute of Medicine several years ago looked at the risk of low dose radiation to the continental United States where people were exposed to very, very low dose radiation and the question was did the risk of screening outweigh the risk of not screening. So you can go through their decision analysis and put in all the numbers, what percentage of people will have medullary, what percent will need surgery and what percent will have side effects. So it will be nice to do it prospectively but you can statistically get a really good feel for how many people would be hurt by the screening program in that decision analysis.

DR. BURMAN: Of course, it would be, and thank you Mike, that would be limited by the number of years of people on the medication, which is relatively short but an inherent problem.

DR. TUTTLE: It would give you the first look at that initial screening, which is the initial thing. If you screened everybody in this previous study, how many would have had surgery and what would it have been like. This is why I voted yes. I just don't see how, if we ask for another years worth of data, if they showed us two years we would ask for three, if they showed us six months, we would ask for two. I mean they showed us one-year data; the calcitonins are not changing and some on out up to two years. So if it's not changing in two years, I can't imagine that it's likely to change in three years or five years so hard to know.

DR. BURMAN: Thank you all. Dr. Parks and Dr. Rosebraugh, any further issues to bring up?

DR. PARKS: No other issues related to the application, if there is nothing, I would just like to make a closing statement on behalf of the FDA.

DR. BURMAN: Of course

DR. PARKS: On behalf of the FDA, I would like to thank all the advisory committee panel members on both days, we really appreciate your very thoughtful and thorough scientific discussion and just as importantly to hear your professional and personal perspectives on the management of Type 2 Diabetes and taking into consideration the safety profile of both these applications. I am somewhat comforted to know that you have struggled with some of the difficult issues that the agency has as well as observed in this vote here. We will take back all your discussion, your recommendations and take on the difficult task now of next steps. So thank you very

much for your participation. I also would like to thank, both applications and both Sponsors yesterday, Bristol-Myers Squibb and today Novo Nordisk. We recognize that you were caught in the middle here and so there was a lot of angst I imagine and you have been very responsive in getting information to us after the FDA guidance was published in December, so we very much appreciate your working with us on that.

I guess that, I know that since December of 2008, in the last four, five months there has been certainly a lot of speculation anxiety in the diabetes community, the medical community, a lot of people and I hope that the advisory committee in the past two days has provided at least some clarity to the difficult issues of the agency and actually the public has to deal with this treatment strategy. Then finally, I would like to thank the FDA staff for both days, for both applications for your excellent work. We really could not do this without you, so thank you.

DR. BURMAN: Thank you. In closing remarks, I would also like to extend my gratitude and the gratitude of the committee to the Sponsor who has been very responsive, had excellent presentations and hope you understand the vote and the intent of the vote and what has been recommended and thank you very much.

I would also like to thank the FDA, Drs. Rosebraugh, Parks, Mahoney and Joffe in particular and Paul Tran for making this job as chair and also for the committee very easy. Thank you to all the committee members for all your hard work as well as to Ms. Killion for being the patient representative. With that, we stand adjourned.

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

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KEYWORD INDEX