FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC)

Wednesday, May 25, 2016

8:00 a.m. to 4:56 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD, NCPS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Daniel Budnitz, MD, MPH

Medical Officer, Division of Healthcare Quality Promotion

Director, Medication Safety Program

Centers for Disease Control and Prevention

Atlanta, Georgia

Brendan M. Everett, MD, MPH

Assistant Professor of Medicine

Harvard Medical School

Director, General Cardiology Inpatient Service

Brigham and Women's Hospital

Boston, Massachusetts

Diana Hallare, MPH

(Consumer Representative)

Visalia, California

James D. Neaton, PhD

Professor of Biostatistics

Division of Biostatistics

School of Public Health

University of Minnesota

Minneapolis, Minnesota

Robert J. Smith, MD

(Chairperson)

Professor of Medicine (Endocrinology)

The Warren Alpert School of Medicine

Professor of Health Services, Policy and Practice

Brown University

Providence, Rhode Island

Charles A. Stanley, MD

Professor of Pediatrics

University of Pennsylvania

Perelman School of Medicine

Division of Endocrinology

Children's Hospital of Philadelphia

Philadelphia, Pennsylvania

Peter W. F. Wilson, MD

Director

Epidemiology and Genomic Medicine

Atlanta Veterans Administration Medical Center

Professor of Medicine and Public Health

Emory University

Emory Clinical Cardiovascular Research Institute

Atlanta, Georgia

Susan Z. Yanovski, MD

Co-Director, Office of Obesity Research

Senior Scientific Advisor for Clinical

Obesity Research

National Institute of Diabetes and Digestive and

Kidney Diseases

National Institutes of Health (NIH)

Bethesda, Maryland

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Reshma Kewalramani, MD

(Industry Representative)

Vice President, US Medical Organization

Amgen

Thousand Oaks, California

TEMPORARY MEMBERS (Voting)

Barbara Berney

(Patient Representative)

Rockford, Illinois

Kenneth Burman, MD

Director, Section of Endocrinology

MedStar Washington Hospital Center

Director, Integrated Endocrine Training Program

MedStar Georgetown University Hospital

Washington, District of Columbia

Timothy S. Lesar, PharmD

Patient Care Service Director

Director of Clinical Pharmacy Services

Albany Medical Center

Albany, New York

Steven B. Meisel, PharmD

System Director of Patient Safety

Fairview Health Services

Minneapolis, Minnesota

Martha C. Nason, PhD

Mathematical Statistician

Division of Clinical Research

National Institute of Allergy and Infectious Diseases, National Institutes of Health

Bethesda, Maryland

Michael D. Reed, PharmD, FCCP, FCP

Director

Rainbow Clinical Research Center

Rainbow Babies and Children's Hospital

University Hospitals Case Medical Center

Cleveland, Ohio

Ellen W. Seely, MD

Professor of Medicine

Harvard Medical School

Brigham and Women's Hospital

Boston, Massachusetts

FDA PARTICIPANTS (Non-Voting)

Mary Parks, MD
Deputy Director
Office of Drug Evaluation II (ODE-II)
Office of New Drugs (OND), CDER, FDA

Jean-Marc Guettier, MDCM
Director
Division of Metabolism and Endocrinology Products (DMEP)
ODE-II, OND, CDER, FDA

Lubna Merchant, MS, PharmD
Deputy Director
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Suchitra Balakrishnan, MD, PhD

Clinical Reviewer

DMEP, ODE-II, OND, CDER, FDA

William Chong, MD

Clinical Team Leader

DMEP, ODE-II, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. SMITH: Good morning. I would like to first remind everyone to please silence your cell phones, smartphones, any other devices that make noise, if you've not already done so. And I'd also like to identify the FDA press contact, Theresa Eisenman. If you're present, Theresa, please -- Theresa is in the back by the door.

My name is Robert Smith. I'm the chairperson of the Endocrinologic and Metabolic Drugs Advisory Committee, and I will be chairing this meeting. I will now call the Endocrinologic and Metabolic Drugs Advisory Committee meeting to order. We'll start by going around the table and introduce ourselves. And we'll start with the FDA to my left, and then make our way around the table.

DR. PARKS: Good morning. I'm Mary Parks. I'm deputy director in the Office of Drug Evaluation II.

DR. GUETTIER: Good morning. My name is Jean-Marc Guettier. I'm the division director in the Division of Metabolism and Endocrinology Products.

DR. CHONG: Good morning. I'm William Chong. I'm a clinical team leader in the Division of Metabolism and Endocrinology Products.

DR. BALAKRISHNAN: Suchitra Balakrishnan, medical officer, Division of Metabolism and Endocrinology Products.

DR. MERCHANT: Hi. I'm Lubna Merchant, deputy director, Division of Medication Error Prevention and Analysis.

DR. BURMAN: Ken Burman, chief of endocrinology at MedStar Washington Hospital Center and professor at Georgetown University.

DR. BUDNITZ: Dan Budnitz, director of medication safety programs, Centers for Disease Control and Prevention.

DR. NEATON: I'm Jim Neaton, professor of biostatistics, University of Minnesota.

DR. LESAR: Timothy Lesar, director of

clinical pharmacy services, Albany Medical Center, Albany, New York.

DR. EVERETT: Hi. Brendan Everett, director of general and patient cardiology at the Brigham and Women's Hospital in Boston and Harvard Medical School.

DR. BONNER: LaToya Bonner, designated federal officer for this meeting.

DR. SMITH: I'm Robert Smith. I'm professor of medicine and endocrinology at the Medical School at Brown University and also a professor in the School of Public Health there.

DR. SEELY: Ellen Seely. I'm an endocrinologist at Brigham and Women's Hospital and Professor of Medicine, Harvard Medical School.

MS. HALLARE: Diana Hallare, consumer representative.

DR. MEISEL: Steve Meisel, a patient safety officer for Fairview Health Services in Minneapolis.

DR. WILSON: Peter Wilson, professor of medicine, Emory University, endocrinology,

prevention cardiology and public health.

DR. STANLEY: I'm Charles Stanley. I'm a pediatric endocrinologist at Children's Hospital of Philadelphia and professor of Pediatrics at the University of Pennsylvania School of Medicine.

DR. YANOVSKI: Susan Yanovski. I'm co-director of the Office for Obesity Research at the National Institute of Diabetes and Digestive and Kidney Diseases.

MS. BERNEY: I'm Barbara Berney. I'm the patient representative.

DR. REED: Good morning. I'm Michael Reed. I'm a pediatric clinical pharmacologist and toxicologist, and I'm director of the clinical research program at Rainbow Babies and Children's Hospital at the University Hospitals Case Western Reserve Medical Center.

DR. NASON: Martha Nason. I'm a mathematical statistician at National Institute of Allergy and Infectious Diseases.

DR. KEWALRAMANI: Reshma Kewalramani. I'm the industry representative and the head of the

U.S. medical organization at Amgen.

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

In the spirit of the Federal Advisory Committee Act and the Government and 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. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass the microphone to Commander LaToya Bonner, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. BONNER: The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee 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's compliance with federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 U.S.C., Section 208 is being provided to participants in today's

meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C., Section 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 a discussion of the safety and efficacy of new drug application 208673 for insulin glargine and lixisenatide injection, a fixed-ratio drug product consisting of insulin and a GLP-1 receptor agonist, and 208471 for lixisenatide injection, a GLP-1 receptor agonist submitted by Sanofi Aventis care of Sanofi U.S. Services Inc., proposed for the treatment of adults with type 2 diabetes mellitus.

This is a particular matters meeting during which specific matters related to Sanofi's new drug application will be discussed. Based on the agenda for today's meeting, and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to

disclose any public statement that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Reshma Kewalramani is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Kewalramani's role at this meeting is to represent industry in general and not any particular company. Dr. Kewalramani is employed by Amgen.

We would like to remind members and temporary voting members that, if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. SMITH: Thank you. So we'll now proceed

with the FDA's introductory remarks from Dr. Jean-Marc Guettier.

FDA Introductory Remarks - Jean-Marc Guettier

DR. GUETTIER: Good morning. Again, my name is Jean-Marc Guettier, and I am the director of the Division of Metabolism and Endocrinology Products at the FDA. I welcome the members of the advisory committee to today's meeting, which was convened to discuss the new drug application for a fixed-combination drug product submitted by Sanofi Aventis for the treatment of adults with type 2 diabetes.

As you know, the product combines a new GLP-1 receptor agonist with a marketed basal insulin. I'd like to take the next 10 minutes to cover the issues raised by the applicant.

So in today's meeting, we will cover two new drug applications. The first application is for a new GLP-1 receptor agonist called lixisenatide. And the second new drug application is for the fixed-combination product combining lixisenatide with insulin glargine.

The major focus of the discussion will be spent on the application for the combination drug, so let me again review the general regulatory framework for combination drugs. Although this was covered in yesterday's meeting, not all advisors were here yesterday, and it's important for the record that I repeat many of the information that was discussed.

The committee should approach this meeting as an entirely new meeting and repeat arguments that are pertinent to this drug and may have already been discussed at yesterday's meeting. Again, it's important that you do this so that these comments and arguments can be entered into the record for this specific application.

Now, for the background information that pertains to combination drugs, the Food and Drug Administration's policy on combination drugs is defined in Title 21 of the Code of Federal Regulations.

The regulation states that two or more drugs can be combined in a single dosage form when each

component makes a contribution to the claimed effects. Thus, a combination drug that has an effect compared to placebo but combines an effective drug with a drug substance that has no effect would not meet the regulatory requirements, because, in this example, the effect would be entirely driven by a single component.

As you have just heard, the rule refers to claimed effects. And for an anti-diabetic combination, the specific topic of today's discussion, the claimed effect is improvement in glycemic control as captured using hemoglobin A1c change. As many of you know, improvement in glycemic control is used as a surrogate for clinical benefit for anti-diabetic products.

For fixed combinations of anti-diabetics, the contribution to the claimed effect is demonstrated either in a factorial study or in what I refer to in this slide as an add-on study. In a factorial study, the glucose-lowering effect of two drugs is compared to the glucose-lowering effect of each individual drug.

Contribution to the claimed effect is demonstrated if the glucose-lowering effect of two drugs is greater than the glucose-lowering effect of each individual drug. For a fixed-dose product, this is generally established through the entire dose range.

In an add-on study design, the glucose-lowering effect that results from adding a new drug to a regimen that includes a maximally effective dose of another drug is evaluated. Contribution to the claimed effect in this setting is determined if addition of the new drug results in improving glucose control more than a placebo or comparator. This scenario assumes that the first drug is still contributing an effect when the second drug is added.

Although both types of studies can be used for the purpose of demonstrating contribution to claimed effect, the sequential add-on trial design may more closely mimic standard clinical care where, in general, a second glucose-lowering drug is added only if, after some period of time,

glucose control remains inadequate on a maximally effective or tolerated dose of a first drug. And it is generally assumed that the first agent is still effective.

Although some therapeutic guidelines advocate initiating dual therapy simultaneously in specific patient populations, there are no empiric data that have rigorously examined the net clinical benefit derived from a strategy that consists of initiating two drugs at once versus an alternative strategy that consists of adding additional drugs only in patients who do not respond to a single, maximally effective drug.

As was seen in the program that will be discussed today, there were some patients in all trials who reached goal on a single agent. Whether the patient would respond to a single agent is an unknown when deciding to initiate dual therapy.

Having covered the contribution to claimed effects concept, I am now going to review the other aspect of the regulation, which applies to combination drugs. The regulation also states that

the dosage of each component in the combination drug must be safe and effective for a significant patient population requiring such concurrent therapy.

This aspect of the regulation deals in part with the clinical rationale for the proposed combination drug. That is, does the combination product make sense from a clinical perspective?

Here, I want to emphasize that the rule is explicit in talking about the actual product itself, with all its limitations.

The first bullet lists example of potential clinical considerations that may be used to decide whether the concept of combining two products is rational, but these questions do not explicitly address the regulation. A combination drug that combines two approved drugs that are already known to be safe and effective when administered concurrently to treat a disease would in theory be rationale.

The second question on this slide addresses the regulation itself and refers to the reality of

the product. It asks whether the proposed dosage offered in the product meets the needs of a significant population requiring concurrent therapy.

A combination product that provides for all approved doses of two marketed products and whose dosage is sufficiently flexible to be both safe and effective for a significant patient population requiring concurrent therapy would satisfy this aspect of the regulation.

On the other hand, a combination product that, by virtue of its dosing inflexibility, would be safe and effective only for an insignificant patient population requiring concurrent therapy would not satisfy this aspect of the regulation.

The committee was convened today to consider the specific limitations of the product proposed and to discuss whether, in light of these limitations, the product would still be safe and effective for a significant patient population requiring concurrent therapy with the two products in the combination.

Let's now turn to the proposed combination product in this application. The proposed combination in this application combines an already marketed active pharmaceutical ingredient, glargine, a basal insulin injected once daily, with a novel active pharmaceutical ingredient, lixisenatide, a glucagon-like peptide 1 receptor agonist, also injected once daily. The active pharmaceutical ingredients will be referred to as drug substances.

As was stated in the previous slide, a legitimate question for any fixed-combination product is, does combining these two active ingredients make clinical sense? In concept, combining the two active ingredients in a single product presentation may not be unreasonable given that basal insulin and GLP-1 agonists are used concurrently in some patients for the treatment of type 2 diabetes.

Before you can assess whether the dosage in the product would be safe and effective for a significant patient population who require

concurrent use, you should have an idea of who would be a candidate for concurrent use.

Therapeutic guidelines do not expressly define this population and, in the care setting, it is a decision left to the practitioner. Nevertheless, for the purpose of addressing the discussions at today's meeting, you'll need to consider who the population of concurrent users will be in light of the limitations of the product.

Would it be all patients failing a first-line agent, only a specific subpopulation of patients failing a first-line agent, only patients inadequately controlled on oral agents and a basal regimen, including either a GLP-1 receptor agonist or a basal insulin, only patients already using both, or all of these patients?

It's important to define the population of concurrent users because, as you will hear on the following slide, the product has limitations in terms of dosing flexibility. And per the regulation, the product should meet the needs of a significant population requiring concurrent

therapy.

For example, in light of the dosage limitations, would it be reasonable to select a population with early disease who only require low doses of the combinations since, at these doses, patients may be exposed to doses of one of the component that provides no benefits?

Alternatively, in a population with severe insulin resistance, the dosage in the combination may not provide long-term glucose control because higher doses of insulin that can be delivered by the combination product will be required.

The applicant has proposed two populations in the two studies they have conducted for the combination product. These are patients not previously treated with either an insulin or a GLP-1 receptor agonist who have failed a first-line agent and patients inadequately controlled on a basal insulin.

Once more, the combination rule states that the dosage of each component in the product has to be such that the combination drug is safe and

effective for a significant patient population requiring concurrent therapy. For this, it's important to consider whether the dosage limitations inherent to the fixed-combination product administered using the two proposed devices, represented here as pen A and pen B, would satisfy this aspect of the regulation.

The figure compares doses of lixisenatide and insulin glargine drug substances in the lixisenatide product proposed for marketing, and in the combination product proposed in this application, and in the insulin glargine product already indicated and marketed for the treatment of type 2 diabetes. The products are compared on the insulin glargine scale of measure, and you will note that the lixisenatide scale is different between pen A and pen B for the fixed-combination product.

You see in the figure that the two drug substances in the combination product are joined and individual titration of each drug substance is not possible. This limitation will constrain the

prescriber's ability to select and titrate the dose of each of the components independently. Efficacy and safety of concurrent use may be affected by this limitation.

A second thing to note is that a patient requiring additional insulin because of inadequate glucose control on pen A will have to undergo a 35 percent reduction in the lixisenatide dose when transitioning to pen B. The clinical logic of going down on the dose of a presumably active drug in a patient requiring additional glucose control is not apparent to us. This limitation will have to be considered.

You could also appreciate from the figure that the individual lixisenatide product proposed for marketing is not dosed on a continuous scale as it is in the combination product, but is dosed at a single discreet dose of 20 micrograms. As you will hear today, doses of less than 20 micrograms have not been established to be effective for the treatment of type 2 diabetes.

You can see that, for the entire

lixisenatide dose range in the combination product, subjects will be receiving doses below 20 micrograms. In addition, the effective dose will be reached only when the maximum insulin dose is reached. It will be important to consider how this limitation would affect how you would use this product.

For example, would you keep a patient on low doses of the combination products for months knowing that, for some doses, benefits of the lixisenatide component may not outweigh the risks? In a patient tolerating a 20-microgram dose of lixisenatide, why would you decrease the dose to start the combination product if you believe the drug is still exerting a glucose-lowering effect?

Finally, Lantus, the insulin glargine drug product indicated for type 2 diabetes, is dosed individually and in theory has no maximally effective dose. This contrasts to the combination product, which is capped at 40 or 60 units, depending on the pen used. How would this limitation impact concurrent use?

The areas highlighted in red are non-overlapping areas and areas we view as problematic for this product. So the central issue raised by this application is, do the differences in dosing between the individual component and the proposed fixed combination raise concerns such that the product would not be safe and effective for a significant patient population requiring concurrent therapy?

So this concludes my introductory remark and the committee is charged with discussing and opining on whether the product administered using the proposed devices would be safe and effective for a significant patient population requiring concurrent therapy with a GLP-1 and a basal insulin.

I want to reemphasize one last time that you will need to consider the specific limitations related to dosing and the proposed delivery device in your deliberation. I'll now turn to the discussion points and the voting question.

In the first discussion point, we ask you to

discuss issues related to the efficacy and safety of the new drug, lixisenatide for the treatment of patients with type 2 diabetes. We ask you to comment on whether any of these issues preclude approval of lixisenatide.

In the second discussion point, we ask you to discuss the benefits of starting the fixed-combination drug product, which contains two drugs, in patients with type 2 diabetes not treated with either a GLP-1 agonist or a basal insulin. And this scenario is starting two new drugs at once. In the clinical care setting, you have a range of options for these patients and one option is to start one of the available agents.

Recall that some GLP-1 agents are available as once-weekly preparations. Please tell us why you would start two drugs at once in these patients and what benefits you would be targeting using this strategy. Keeping in mind the issues of dosing, please describe the patient population in whom you would recommend this product.

In the third discussion point, we ask you to

discuss the benefits of using the fixed-combination product in patients who may already be on either a GLP-1 agonist or a basal insulin. Here, you're adding a single drug to the regimen. And again, keeping in mind some of the limitations of the dosing, who would be a candidate for this therapy and why?

In the fourth discussion point, we ask you to discuss your level of clinical concerns related to the fact that the product combines a drug that, when used alone, has a wide effective dose range and is titrated to effect on a continuous scale with a drug that, when used alone, has 1 or 2 recommended effective dose. We'd like you to specifically discuss issues related to loss of dosing flexibility and issues related specifically to product presentation and devices.

The final question asks you whether, in light of all the data in the briefing materials, presentations and discussions, you would recommend approval of the fixed-combination drug delivered using the proposed devices for the treatment of

patients with type 2 diabetes. We recognize that your answer in discussion point 1 may influence how you vote on this question.

If you vote yes, please provide your rationale for the recommended patient population and recommend additional post-approval studies if you think these are needed. If you vote no, please provide your rationale and recommend additional pre-approval studies if you think these are needed. And that concludes my part of the presentation. Thank you.

DR. SMITH: Thank you.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of

any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interests in a sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. And so we'll now proceed with Sanofi's presentations.

Applicant Presentation - Paul Chew

DR. CHEW: Mr. Chairman, members of the committee, and members of the Food and Drug Administration, good morning. On behalf of Sanofi, I'd like to thank the FDA and the committee for reviewing the data on lixisenatide and the fixed-ratio combination of lixisenatide and Lantus, or iGlarLixi.

My name is Paul Chew, and I'm senior vice-

president, research and development, at Sanofi. We're here today seeking the committee's endorsement for approval of lixisenatide and iGlarLixi for the treatment of adults with type 2 diabetes. Previously, we referred to iGlarLixi as LixiLan. Our presentations today will focus both on lixisenatide and iGlarLixi, as they're both under consideration for approval.

We recognize that this is a unique situation and that our candidate iGlarLixi is the combination of two products, the first being FDA-approved Lantus, a well-established insulin glargine, and the second, lixisenatide, a GLP-1 receptor agonist, which is under review by FDA.

Let me provide some brief background on Lantus before discussing the rationale and indications for lixisenatide and iGlarLixi. Lantus was approved in the U.S. and Europe in 2000. It's been marketed worldwide since that time. Extensive safety data are available for Lantus and Lantus has been the global standard of long-acting basal insulins for more than 15 years.

ORIGIN studied the effects of Lantus on cardiovascular events in more than 6,000 Lantus-treated patients and showed that Lantus was safe in people with diabetes and did not increase cardiovascular risk. But as with any insulin, glucose control comes with a price of weight gain and the risk of hypoglycemia.

Lixisenatide was developed to improve glycemic control in adults with type 2 diabetes, but without the weight gain and hypoglycemia seen with insulin. Lixisenatide was granted marketing authorization in Europe in 2013. It's been subsequently approved around the world.

The lixisenatide NDA was submitted in 2015 after completion of our long-term cardiovascular outcomes study, ELIXA. It's important to note that the cardiovascular safety has been shown in two completed outcomes trials for both Lantus and lixisenatide. The following indication has been submitted for lixisenatide. Lixisenatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2

diabetes mellitus.

Now, let me provide some background on iGlarLixi. iGlarLixi is a novel approach to controlling blood glucose. The rationale for iGlarLixi was to achieve target A1c without increasing the risk of hypoglycemia or weight gain seen with insulin alone and better GI tolerability than seen with GLP-1 monotherapy.

As you'll hear in our presentation, combining Lantus with lixisenatide in one product achieves these goals by addressing both components of hyperglycemic burden, fasting as well as post-prandial glucose, with one injection.

iGlarLixi will be available in two fixed ratios of Lantus to lixisenatide, 2 or 3 units of Lantus per microgram of lixisenatide in order to provide coverage for a wide range of patients with diabetes.

iGlarLixi will be for patients who are uncontrolled on oral anti-diabetic therapies and who need to make a decision about their first injectable treatment. And iGlarLixi will also be

for patients on basal insulin who have failed to achieve a target A1c despite optimizing their insulin dose.

iGlarLixi allows administration of doses of lixisenatide between 5 and 20 micrograms, depending on the dose of Lantus, which is the same familiar way physicians titrate Lantus today, according to the fasting plasma glucose.

The proposed indication for iGlarLixi is as follows. Insulin glargine lixisenatide fixed-ratio combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

Our agenda for the rest of our presentation is as follows. Dr. Neil Skolnik will discuss the need for new treat options for type 2 diabetes. Dr. John Newton will review a mechanism of action and pharmacodynamic properties of lixisenatide and iGlarLixi.

Dr. Rachele Berria will present the efficacy data, and Dr. Kristen Sharma will review the safety

data for lixisenatide and iGlarLixi. Dr. Rene Belder will provide our perspective on the FDA points to consider. Finally, Dr. Luigi Meneghini will present the overall risk-benefit profile. I'll then return to the lectern to answer your questions.

We also have additional experts with us today to help answer your questions. The external experts have been compensated for their time and travel. Thank you. And I'll now turn the lectern to Dr. Skolnik.

Applicant Presentation - Neil Skolnik

DR. SKOLNIK: Hello. I'm Neil Skolnik. I'm a Professor of Family and Community Medicine at Temple University School of Medicine. And I'm an Associate Director in the Family Medicine Residency at Abington-Jefferson Health. Most of all, though, I'm a family doctor who takes care of many patients with diabetes.

Primary care physicians like myself take care of over 90 percent of all the patients with diabetes in the United States. And despite all the

recent advances, there remain unmet needs, especially for patients who are not at goal and who need injectable therapies. And we need to do better for them.

I want to discuss the challenges that we as primary care physicians face, which might be improved by new therapeutic options for our patients with diabetes.

We need to do better because the discussion today occurs in the context of the fact that almost half of all patients with diabetes do not have their blood sugars controlled to their A1c goals. And I can tell you it's not because we don't try.

So we have to ask ourselves the question, why is this is the case? Is it because we don't recognize the importance of treating to goal? That's not the case. We've known for years that reaching A1c goals is important in order to reduce the risk of vascular complications, including kidney failure, retinopathy, MI, and stroke.

So what are the reasons that patients don't achieve their A1c goals? Those reasons essentially

fall into two categories, first, failure to address post-prandial hyperglycemia and, second, therapeutic inertia. In order to get patients to their A1c targets, we need agents that address both fasting and post-prandial blood glucose levels.

These graphs show the relative contributions of both fasting plasma glucose and post-prandial or after-meal hyperglycemia to A1cs across a range of values in patients not well-controlled on oral agents or on basal insulin. As you can see, a significant portion of the A1c excursion is accounted for by post-prandial hyperglycemia, which needs to be addressed to achieve A1c control and which is simply not well addressed with most of our current agents.

Let us now go over the current medications and an approach to treating hyperglycemia in type 2 diabetes. There have been significant advances in glucose-lowering therapy over the last 15 years. Each of our options for treatment, as you can see in this chart adapted from the ADA guidelines,

comes with varying efficacy and varying side effects. Unfortunately, many of the same medications that we prescribe to lower blood sugars work against our goals of weight loss and our efforts to minimize hypoglycemia.

So how do we treat patients today? The current American Diabetes Association guidelines provide an approach for treatment commonly used by primary care physicians. In this algorithm, there is a stepwise progression for the treatment of diabetes. We start with metformin and then add additional medications as needed to achieve glucose control.

As the algorithm progresses, treatment regimens become more complex and include more oral medicines and more injections. The reality is that the progressive nature of type 2 diabetes requires us to change medications and adjust doses on a regular basis.

Eventually, we add basal insulin or a GLP-1 agonist, and then if needed, prandial insulin as well. The addition of prandial insulin on top of

basal insulin requires more injections, more frequent glucose monitoring, may require carb counting, and causes simply disruption in our patients' lives.

For these reasons, many patients resist the addition of mealtime insulin. The two-injection approach of the basal insulin and a GLP-1 agonist requires multiple injections while tolerating a high incidence of GI side effects, which are both barriers to initiating and adhering to treatment in these difficult to treat patients. Patients and doctors are slow to intensify therapy because of this complexity, and that leads to therapeutic inertia.

Let me give you an example of one of my patients with type 2 diabetes who is similar to patients that all of us as clinicians see every day. I've known Betty for 20 years. Her diabetes was under control when I met her and for a few years after that. But after a few years, her sugars began to deteriorate.

It took me three years to convince her to

add insulin, and then again her sugars were under control for a little while, and then again they began to deteriorate. I've not been able to get her to start a second injection, either prandial insulin or a GLP-1, leaving her at unnecessarily increased risk of complications due to her persistently elevated A1c.

I tell this story not because it's dramatic, but because it's ordinary. A former poet laureate of the United States wrote a poem titled, "From the Beating End of the Stethoscope." What he meant by that title is that it's essential for us as physicians to view care from the patient's point of view.

Treatment complexity, fear of additional medications, fear of needles, fear of weight gain and hypoglycemia, as well as the desire not to use multiple injections or check their blood sugars multiple times during the day all contribute to clinical inertia and all are relevant to patients in their decisions about whether to advance therapy or to stay with their current medications.

In summary, I discussed a few minutes ago that over 50 percent of our patients with type 2 diabetes do not reach their A1c targets and that we can do better, particularly for our patients who are not at goal on oral medications or on basal insulin.

We need new medications that meet the challenges to adequately control A1c levels, including medications that help patients achieve better A1c control by addressing both fasting plasma glucose and post-prandial glucose, and that combat clinical inertia by simplifying patients' injectable regimens, by mitigating weight gain, by minimizing the side effects such as GI intolerance, and minimizing hypoglycemia.

By accomplishing these goals, we should be able to achieve better glucose control for the many patients who currently are not at their A1c goals and who remain at unnecessarily elevated risk for complications from their diabetes.

Thank you for your attention, and I will now turn our discussion over to Dr. John Newton.

Applicant Presentation - John Newton

DR. NEWTON: Thank you, Dr. Skolnik. I'm John Newton, head of pharmacokinetics, dynamics, and metabolism at Sanofi. I'll now provide a brief presentation on the pharmacodynamics of lixisenatide and iGlarLixi.

Recognizing the needs of patients, as described by Dr. Skolnik, we realized that combining the effects of basal insulin and lixisenatide in a single injection could provide a more beneficial profile, one that patients and physicians were looking for.

To elaborate on this, I will describe the complementary actions of lixisenatide and Lantus. Lixisenatide lowers blood glucose by three well-defined mechanisms; delayed gastric emptying resulting in reduced glucose absorption post-meal, the stimulation of insulin secretion, and the inhibition of glucagon secretion.

These actions of lixisenatide are meal or glucose dependent and therefore associated with a low risk of hypoglycemia. As a result of these

characteristics, lixisenatide is effective in lowering post-prandial blood glucose. In addition, lixisenatide reduces weight with chronic administration.

When considering the actions of lixisenatide, it is important to understand how these actions complement or contrast to the effects observed with Lantus as the second component of iGlarLixi. Lantus lowers blood glucose through a variety of mechanisms. Some of these include increased uptake of glucose by muscle, increased hepatic uptake of glucose, and decreased glucose synthesis, increased uptake of glucose by adipose tissue.

Unlike lixisenatide, these mechanisms of glucose lowering are glucose independent and, with it, lower the risk of hypoglycemia. Furthermore, Lantus use can lead to weight gain, especially at higher doses.

The primary glucodynamic effect of Lantus is on fasting plasma glucose rather than post-prandial glucose. This is an important point, as post-

prandial glucose levels can be utilized to measure the pharmacodynamic response of lixisenatide administered alone or as part of the fixed-ratio combination, iGlarLixi.

The combination of both lixisenatide and Lantus in iGlarLixi represents a novel therapeutic approach to addressing the medical need of simultaneous reduction of both fasting and post-prandial glucose. Because lixisenatide does not markedly impact fasting plasma glucose, the well-established titration approaches for Lantus can be applied for titration of iGlarLixi, and is the basis for the use of Lantus units in the dosing of iGlarLixi.

On the next few slides, I will focus on describing the key pharmacodynamic property of lixisenatide, the reduction in post-prandial glucose levels, then focusing on the impact of lixisenatide dose on this effect and the reduction in A1c.

Lixisenatide produces a significant and sustained delay in gastric emptying, which prolongs

the absorption of meal derived glucose and blunts elevation in post-prandial glucose levels. Here, we see the effect of different daily doses of lixisenatide given in an escalating fashion on post-prandial glucose levels after a standardized meal in patients with type 2 diabetes.

The orange line shows baseline glucose levels following a standardized meal prior to starting the course of lixisenatide treatment. And the blue represents post-prandial glucose levels following a 20-microgram dose of lixisenatide. At this dose, lixisenatide produces a nearly complete suppression of post-prandial glucose excursion after ingestion of a meal.

At a dose of 10 micrograms, indicated by the green line, lixisenatide also showed a similar pattern of post-prandial glucose reduction. Finally, a 5-microgram dose, indicated by the black line, provided a significant post-prandial glucose-lowering effect.

This slide describes the quantitative relationship of lixisenatide dose to post-prandial

glucose reductions after a standardized meal following different doses ranging from 5 to 20 micrograms. The grey line represents the placebo group. The blue line represents the lixisenatide group.

Maximal reductions in post-prandial glucose area under the curves were achieved by 12.5 micrograms and above. At doses of 7.5 to 10 micrograms, we see approximately 80 percent of the maximal post-prandial glucose AUC reduction, while at 5 micrograms we see approximately 50 percent of the post-prandial AUC reduction observed with 20 micrograms.

These dose relationships with post-prandial glucose reduction were the conceptual basis for our decision to develop iGlarLixi over a lixisenatide dose range of 5 to 20 micrograms, as patients would have post-prandial control over a wide range of Lantus doses.

I'll now illustrate the impact of lixisenatide dose on A1c. This slide presents A1c and responder rate data from a phase 2 dose ranging

study in patients with type 2 diabetes on metformin where various doses of lixisenatide, ranging from 5 to 30 micrograms, were evaluated over 13 weeks.

In the left-hand panel, we see that near-maximal changes from baseline on A1c were observed with once-daily doses of 20 micrograms and above. Furthermore, the placebo-subtracted mean reduction in A1c for a 5-microgram once-daily dose was nearly 60 percent of the response observed at 20 micrograms.

In the right-hand panel, we show the percentage of patients reaching target A1c levels of less than 7 percent at various doses of lixisenatide. Again, the maximal effect was observed by 20 micrograms of lixisenatide, more than doubling the responder rate compared to placebo. As with A1c, responder rates of 5 micrograms were approximately half of the maximal effect observed at 20 micrograms.

Considering these data, balancing maximal efficacy and patient adherence, with acceptable tolerability, the dose and regimen selected for

lixisenatide as a single agent was 20 micrograms once daily.

For further development of iGlarLixi, the dose range selected for lixisenatide was 5 to 20 micrograms because daily doses as low as 5 micrograms provided a clinically meaningful improvement in post-prandial glucose and efficacy as measured by a change in baseline in A1c or A1c responder rates.

Doses above 20 micrograms did not offer further clinically meaningful improvement in either post-prandial glucose or overall glycemic efficacy. Furthermore, tolerability decreased due to increased GI side effects and treatment related discontinuation rates.

In the selection of the most appropriate fixed-ratio combination or combinations for iGlarLixi to meet the needs of our patient population, multiple clinical considerations were addressed.

For Lantus, a dose of 10 units was needed at the low end of the fixed-ratio combination dose

range as this is the standard initiation dose of Lantus in insulin-naïve patients. At the high end of the combination dose range, we wanted to provide a Lantus dose high enough to cover the needs of the majority of the patients.

For lixisenatide, at the low end of the range, a dose of 5 micrograms is needed as this is a dose which resulted in significant reductions in post-prandial glucose and clinically meaningful changes in A1c.

At the high end of the range, we wanted to provide a dose of lixisenatide up to but not exceeding 20 micrograms, which is the dose which had the greatest wealth of benefit-risk information.

Finally, we wanted to be able to initiate patients already on basal insulin therapy with iGlarLixi at the highest initiation dose of 10 micrograms of lixisenatide with a limited and temporary reduction in their insulin dose when compared to their dose used prior to the initiation of the fixed-ratio combination.

The optimal approach to provide the greatest opportunity for patients to receive the full benefits of both drugs was to utilize two fixed-ratio combinations. The 2:1 ratio included in pen A provides a Lantus dose range of 10 to 40 units over a lixisenatide dose range of 5 to 20 micrograms. The selection of the 2:1 ratio was driven by two factors; the Lantus dose of 10 units, which is required for the initiation of insulin-naïve patients, and the lowest effective dose of lixisenatide of 5 micrograms.

The upper end of this fixed-ratio combination was dictated by 20 micrograms of lixisenatide. At a 2:1 ratio, this provides a high dose of 40 units of Lantus for pen A. This is the pen that insulin-naïve patients would initiate therapy on as this provides the recommended starting dose of 10 units of Lantus.

The 3:1 ratio included in pen B provides a Lantus dose range of 30 to 60 units over a lixisenatide dose range of 10 to 20 micrograms. The selection of the 3:1 ratio again was driven by

two factors; the high dose of Lantus of 60 units, which meets the needs of the majority of the patient population, and the highest dose of lixisenatide of 20 micrograms.

The low end of this pen was set at 10 micrograms of lixisenatide as this is the highest recommended initiation dose. At a ratio of 3:1, the low end of this pen provided a Lantus dose of 30 units. This is the pen which could be utilized to initiate patients on higher doses of basal insulin as this pen offers higher doses of Lantus at the recommended highest initiation dose of 10 micrograms of lixisenatide.

Both of the pens that I have described are similar to the well-established SoloSTAR pen that has been utilized for Lantus for many years. Together these two fixed-ratio combinations offer the greatest range of Lantus doses, while providing a clinically meaningful dose of lixisenatide and offers the latitude to minimize insulin dose reduction while initiating dosing in patients with basal insulins.

To summarize the important points regarding the complementary pharmacodynamics of the two components of iGlarLixi, lixisenatide lowers blood glucose by multiple meal- or glucose-dependent mechanisms and is therefore associated with a low risk of hypoglycemia.

A hallmark of lixisenatide's glucodynamic activity is a significant reduction in post-prandial glucose, which is evident over the dose range of 5 to 20 micrograms that is utilized in iGlarLixi.

Lantus lowers blood glucose by glucose independent mechanisms and is therefore associated with a risk of hypoglycemia. Lantus use leads to weight gain, especially at higher doses. A hallmark of Lantus' glucodynamic activity is a reduction in fasting glucose.

The combination of both lixisenatide and Lantus in iGlarLixi as two fixed-ratio combinations represents a novel therapeutic approach to addressing the medical need of simultaneous reduction of both fasting and post-prandial glucose

in a patient population that has broad insulin requirements.

I thank you for your consideration. I will now turn the lectern over to Dr. Rachele Berria.

Applicant Presentation – Rachele Berria

DR. BERRIA: Thank you, Dr. Newton. Good morning. I'm Dr. Rachele Berria. I'm the vice president and head of the diabetes medical unit at Sanofi. Sanofi conducted a robust clinical development program to evaluate the efficacy and safety of lixisenatide. More than 13,000 patients were enrolled in the phase 2 and 3 studies, with approximately 60 percent of them on therapy for at least 1 year.

In addition to the large lixisenatide development program, iGlarLixi was also further evaluated in two large phase 3 studies, one in patients uncontrolled on oral anti-diabetic medications, study 404, and one in patients on basal insulin requiring treatment intensification, or study 405.

These studies were designed and discussed

with FDA in order to support the approval of a combination product, iGlarLixi. Today, I will briefly summarize the key aspect of the lixisenatide phase 3 program, and I will then discuss the results of the iGlarLixi phase 3 studies.

This graph summarizes the mean change in A1c from baseline at the end of the main treatment period for lixisenatide in the blue bar versus placebo in the grey bar or active comparator in the hashed bar. As you can see, lixisenatide was superior to placebo in monotherapy trials. When added to oral medications, lixisenatide was superior to placebo and non-inferior to twice daily lixisenatide with respect to A1c reduction from baseline.

In trials where it was added to basal insulin, lixisenatide also demonstrated superiority to placebo. Across clinical studies, we saw differences in A1c versus placebo between 0.3 and 0.9 percent for the prespecified primary analysis. Also sensitivity analysis showed consistent

results.

Additionally, a number of trials included a double-blind, long-term extension period. The data in this slide are from a trial where lixisenatide was added to metformin as an example of a study describing long-term trends of means for observed A1c reductions. Although not formally analyzed for treatment comparisons, these descriptive results show that larger A1c reductions from baseline tended to occur early for lixisenatide and were sustained throughout 76 weeks.

A key clinical feature of lixisenatide is a pronounced post-prandial glucose lowering, which, as shown here, was observed consistently across the disease spectrum and the various background therapies. In one of the lixisenatide trials where we compared lixisenatide to prandial insulin, either given once daily or three times daily, we demonstrated non-inferiority of lixisenatide with respect to A1c reduction from baseline, which was the primary endpoint of the study.

In this same trial, lixisenatide also

reduced body weight as opposed to a body weight increase in both prandial-insulin-based regimens. Moreover, fewer patients treated with lixisenatide experienced symptomatic hypoglycemic events versus once or three times-a-day prandial insulin. Those trials showed that lixisenatide is a valuable therapeutic alternative to prandial insulin when basal insulin intensification is needed.

Looking at the simplified diabetes treatment guidelines as presented by Dr. Skolnik, lixisenatide would fit right in as a combination with metformin, with or without other oral medications or, as shown in numerous trials, as additional therapy to basal insulin and metformin. The beneficial effects of lixisenatide in combination with basal insulin form the basis of the development of iGlarLixi, of which I will now discuss the efficacy.

Overall, results from our studies show that iGlarLixi improves glucose control of Lantus or lixisenatide alone. In the iGlarLixi pivotal studies, the primary endpoint was change from

baseline in A1c at week 30, which was analyzed using a mix-effect model with repeated measures, including all data, regardless of treatment discontinuation or rescue.

The percentage of patients with missing A1c data at week 30 was less than 6 percent, and similar between groups. We conducted sensitivity analysis for iGlarLixi following the 2010 NRC report and found them consistent with the overall results. Currently, patients who cannot manage their diabetes despite oral anti-diabetic medications can either start a GLP-1 agonist or a basal insulin. Each comes with advantages and disadvantages.

I will now show you how with iGlarLixi it is possible to start with both treatments at the same time and achieve better glycemic control while also mitigating some of the disadvantages of each therapy.

Study 404 was a 3-arm trial comparing iGlarLixi with Lantus and lixisenatide in patients inadequately controlled on metformin alone or

metformin and another oral AD. After screening, patients entered a 4-week run-in phase, which was critical to optimize the background metformin therapy and ensuring the quality of our results. Patients were then randomized to 1 of the 3 open-label treatment arms and followed for 30 weeks. The primary endpoint was change from baseline in A1c at the end of treatment.

Based on demographics, we're well balanced across treatment groups. The overall population was distributed similarly by gender and was predominately Caucasian, with a mean age around 55 years. Most patients were obese, as the baseline BMI was over 30 kilograms per square meter.

Baseline characteristics related to diabetes were comparable among the treatment groups. Overall, the mean duration of diabetes was approximately 9 years, and patients had been using oral medications for about half that time. Both study objectives were met by demonstrating superiority over lixisenatide at not just non-inferiority versus Lantus, but in fact showing

statistically significant greater reductions in A1c compared to Lantus.

The A1c level at screening was 8.2 percent and decreased to 8.1 percent at baseline prior to randomization. After 30 weeks of treatment, A1c levels had reached a value of 7.3 percent for the patients treated with lixisenatide, while the Lantus arm reached an A1c of 6.8 percent at week 30. In the iGlarLixi group the change from baseline was a reduction of 1.6 percent to a final A1c level of 6.5 percent.

Looking at treatment success, we were able to see that a higher proportion of patients in the iGlarLixi group, 74 percent, reached an A1c target of less than 7 percent. This compares favorably to the percentages reached with the individual components.

Let's now look at the results for the key secondary endpoints in this study. We chose these endpoints for our discussion as they are informative with respect to the contribution of lixisenatide and Lantus to the overall benefit in

A1c that their fixed-ratio combination provides over its individual components.

Here, we were able to see a robust change from baseline in fasting plasma glucose levels in both the iGlarLixi and Lantus groups, with a negligible difference between the 2 arms, indicating the predominant contribution of Lantus to fasting plasma glucose levels.

With respect to the effect on post-prandial glucose excursions instead, we observed a different pattern. The effects of lixisenatide on post-prandial glucose excursions are robust and clearly evident in the iGlarLixi arm of the study. This provides a basis of the superior glycemic control observed with iGlarLixi compared with Lantus.

With respect to body weight, we saw the opposite effect of Lantus and lixisenatide. Lantus increased body weight by a little over a kilogram, while iGlarLixi led to a small decrease in body weight. This difference was almost 1.5 kilograms and was statistically significant. The

lixisenatide component in iGlarLixi mitigates the weight gain seen with Lantus.

Another important aspect is the improved gastrointestinal tolerability of iGlarLixi relative to lixisenatide. I would like to draw your attention to the incidence of nausea observed in the 3 treatment groups. The lower rates of nausea with iGlarLixi relative to lixisenatide further support the clinical utility of this treatment strategy.

Our second phase 3 study was done in patients who despite being on insulin needed treatment intensification. Currently, for these patients, we have the choice of adding a second injection of either prandial insulin or a GLP-1 agonist. I will now show you the benefits that can be achieved by replacing the once-daily basal insulin injection by once daily iGlarLixi.

Study 405 was a 2-arm trial comparing iGlarLixi with Lantus in patients who were inadequately controlled despite basal insulin with or without 1 or 2 oral anti-diabetic medications.

It is important to note that, after screening, patients entered a 6-week run-in phase during which they were treated with Lantus, therapy was optimized, and only metformin was to be continued. After the run-in period, patients were randomized to receive iGlarLixi or to continue with Lantus for 30 weeks.

During the treatment period, both therapies were titrated to fasting SMPG targets. However, the Lantus dose in both arms was capped at 60 units per day. For patients requiring rescue therapy, prandial insulin was used. The primary endpoint was change from baseline in A1c and the efficacy hypothesis we tested was statistical superiority of iGlarLixi versus Lantus.

Based on demographics, we're well balanced across treatment groups and with similar profile as we had seen in study 404. With respect to disease characteristics in study 405, duration of diabetes was longer than in study 404 and was around 12 years. These patients had been using insulin for approximately 3 years. Overall disease

characteristics were well balanced in this study.

I will now show you the results of this study. Study 405 also met its primary endpoint by demonstrating statistical superiority over Lantus for change from baseline in A1c. During the run-in, Lantus was titrated, resulting in the screening A1c to fall from 8.5 to a little less than 8.1 percent. And during the 30 weeks of treatment, A1c further decreased to 7.5 percent with Lantus and to 6.9 percent with iGlarLixi. This difference was statistically significant.

As can be seen on this slide, more than half of these very difficult to treat patients achieved an A1c less than 7 percent while on Lantus only a third of the population studied achieved this goal. The contributions of Lantus and lixisenatide to the overall superior glycemic efficacy can be demonstrated by the effects on fasting and post-prandial glucose.

In study 405, there was a small balance between the group decreased from baseline in FPG. And this is because, after the Lantus lead-in

period, only patients who had achieved a mean fasting SMPG level of less than 140 milligrams per deciliter were eligible for randomization. Similarly to study 404, the effects of post-prandial glucose excursions demonstrated the lixisenatide contribution to the overall glycemic efficacy of iGlarLixi.

With regard to body weight, while the Lantus arm led to body weight gain, iGlarLixi showed body weight loss. The treatment difference was almost 1.5 kilograms and was again statistically significant. Therefore, the lixisenatide component in iGlarLixi mitigates the weight gain seen with Lantus.

In summary, the iGlarLixi registration program consisted of two phase 3 pivotal studies in almost 2,000 patients. In these trials, we demonstrated superior glycemic control of iGlarLixi compared to lixisenatide and Lantus in patients uncontrolled on oral medications, as well as versus Lantus in patients treated with basal insulin requiring intensification. The superior glycemic

efficacy of iGlarLixi was clinically meaningful as indicated by the greater number of patients achieving treatment success.

In addition, the lixisenatide component in iGlarLixi led to either body weight loss or mitigation of the body weight gain, which is typically seen with the use of basal insulin, while the incidence of gastrointestinal side effects was lower than the one that was observed with lixisenatide.

The results of our program are robust for all key endpoints and multiple sensitivity analyses. On the basis of this finding, we demonstrated that the contribution of the two components of iGlarLixi meets the FDA requirement for combination products.

I now thank you for your attention and I will hand it over to Dr. Sharma.

Applicant Presentation - Kristen Sharma

DR. SHARMA: Good morning. I'm Kristen Sharma, and I'm the head of the global diabetes and cardiovascular pharmacovigilance unit at Sanofi. I

will be presenting the safety data for lixisenatide and for iGlarLixi. The safety of Lantus, the basal insulin component of iGlarLixi, has been well established in more than 37,000 adult patients with diabetes enrolled in clinical trials.

This experience also includes ORIGIN, our large cardiovascular outcomes trial, that confirmed the long-term cardiovascular safety in more than 6,000 patients treated with Lantus and 89 million patient-years of post-marketing experience worldwide. However, due to time constraints, the current presentation will only focus on lixisenatide and iGlarLixi.

During my presentation today, I will provide an overview of general safety from the two clinical programs, discuss adverse events of interest relevant to the GLP-1 agonist class, and finally highlight key findings from ELIXA, our large cardiovascular outcomes trial with lixisenatide.

For lixisenatide, the safety database included more than 7800 patients in 20 phase 2 and phase 3 studies, providing an extensive cumulative

exposure of more than 10,000 patient-years. This large dataset has been primarily used to characterize the infrequent events of interest. Key subsets include the following. The 9 phase 3 placebo-controlled double-blind efficacy studies make up the primary data pool used to assess general safety. ELIXA was used to evaluate cardiovascular safety and also provided substantial data on longer duration use and patient subpopulations.

For iGlarLixi, the phase 3 safety dataset included 834 iGlarLixi-treated patients. Adverse events of special interest were analyzed from the combined phase 2 and phase 3 data, which included 995 patients. All three studies in this data pool were randomized active control trials of at least 24 weeks duration.

Turning now to adverse events, in the 9 lixisenatide phase 3 placebo-controlled studies, the percentages of patients with any adverse event and with events leading to discontinuation were higher with lixisenatide, reflecting an increase in

GI events versus placebo. However, the rates of serious events and deaths were low and comparable between groups.

With iGlarLixi, a smaller difference in AEs and discontinuations was observed between iGlarLixi and Lantus, and both were lower than lixisenatide, primarily reflecting the attenuation of GI side effects with the combination product. Serious events and deaths were again similar across treatment arms.

As seen with other members of the class, nausea and vomiting were among the most commonly reported events with lixisenatide and were typically of mild or moderate severity. A similar pattern of common events was seen with iGlarLixi, shown here in light blue, but with notably less nausea and vomiting than lixisenatide.

The incidence of hypoglycemia was largely dependent upon the background therapy administered. When given as monotherapy, the incidence of symptomatic hypoglycemia was similar to placebo. A small increase in hypoglycemia was observed when

lixisenatide was added to metformin. However, as shown in the active comparator study with exenatide, this risk was similar to that seen with the twice daily GLP-1 agonist.

Hypoglycemia increased in patients taking background sulfonylurea or basal insulin therapy. And as has been described with other members of the class, the addition of lixisenatide to either of these therapies alone had a modest impact while the greatest effect was seen when lixisenatide was added to a basal insulin plus a sulfonylurea. For this reason, as with currently marketed GLP-1 agonists, it would be reasonable to consider lowering the dose of concurrent sulfonylurea or basal insulin when starting lixisenatide to reduce this risk of hypoglycemia.

Turning now to iGlarLixi, as you will recall, study 404 was performed in insulin-naïve patients inadequately controlled on oral therapy. In this study, the frequency of patients with documented symptomatic hypoglycemia was comparable between iGlarLixi and Lantus and, as expected, was

less frequent with lixisenatide. In study 405, which enrolled patients sub-optimally controlled on basal insulin, higher but balanced rates of hypoglycemia were seen.

Next, I would like to discuss adverse events of interest. A number of safety topics have been described as either identified or potential effects for the class, and these have been evaluated in our development program.

GI effects and hypoglycemia were similar to the effects seen within the class. Injection-site reactions were infrequent, generally mild or moderate in intensity, and rarely led to drug discontinuation. And no signal for pancreatitis or thyroid malignancy were observed with either drug.

Although we were reassured by the lack of significant differences with respect to either general safety or the known GLP-1 class effects, we did observe a difference in allergic reactions in the phase 2 trials. This led us to take the extra step of establishing an allergic reaction adjudication committee to further evaluate these

events. This committee of three independent allergy experts provided a prospective, standardized and blinded adjudication of the suspected allergic events.

The ARAC was charged with three key tasks; to confirm and categorize these events, to grade the event severity, and to assess the likely relationship to study drug. The ARAC used the five prespecified diagnostic categories shown here; urticaria, angioedema, anaphylactic reaction, anaphylactic shock, and other for an allergic event not consistent with the previously defined categories.

It is important to note that the definition of anaphylactic reaction used in this clinical program, although based upon Sampson's criteria, did not require a case to contain the hallmark features generally ascribed to this event, such as hypotension or respiratory compromise. As a result the adjudicated events, while clinically important, frequently did not meet a threshold of clinical severity that is typically associated with

anaphylaxis.

These were designated events of interest, and investigators were directed to report all suspected allergic events. From the more than 400 patients with events that were sent for adjudication, approximately one-third in both treatment groups had confirmed allergic events.

The majority of events occurring in either treatment group were attributed to identified causes other than study drug. Possibly related allergic reactions, although infrequent, were more common with lixisenatide. Among these 29 lixisenatide reactions, urticaria and other non-serious cutaneous reactions were the most common events. However, an imbalance in adjudicated anaphylactic reaction or shock was observed.

In addition, a single anaphylactic reaction was reported in a lixisenatide-treated patient in iGlarLixi study 404. Thus, in the combined programs, including more than 9,000 patients treated with either drug, a total of 11 cases of

possibly related, adjudicated anaphylactic reaction or shock were identified with lixisenatide, while no anaphylactic reactions were reported with iGlarLixi.

Among the 11 cases, 4 were assessed by the reporting investigator as non-serious and resolved rapidly with antihistamine or single-dose corticosteroid treatment. In three additional cases, the patients presented with medically important signs and symptoms of hypersensitivity. However, the cases did not meet Sampson's or NIAID criteria for anaphylaxis. Of note, these 3 cases also resolved following treatment in an outpatient setting.

In the remaining 4 cases, case details were consistent with a clinically severe anaphylactic reaction. The first was a report of IgE negative anaphylactoid shock occurring 10 minutes after the first dose of lixisenatide and which was complicated by concurrent silent MI. The other three anaphylactic reactions, shown here, also resolved rapidly with appropriate therapy. No

deaths due to hypersensitivity occurred in either program.

In order to further assess this small numerical imbalance of 4 cases to none seen in the trials, and in the context of marketed GLP-1 agonists, Sanofi also performed a review of the literature. In this review, a search of the MEDLINE and Embase databases was performed using the search terms shown here. Given the very low incidence rate for true anaphylaxis, the review was focused on publications with a sample size large enough to reasonably assess this rare event.

To provide parity to the published studies, for lixisenatide, we have included suspected drug-related reactions as reported by the investigator, in other words, without the impact of adjudication. Four relevant publications were identified.

The first two were post-marketing nationwide voluntary physician registries performed to assess the use of exenatide and liraglutide in the U.K. The third described 9 pooled phase 2 and phase 3 randomized controlled trials. And the fourth was a

post-marketing registry from Italy, collecting use data for exenatide and other diabetes therapies. The last row presents the anaphylactic drug reactions from the lixisenatide studies.

As shown here, the incidence of anaphylaxis across these publications varied from 0 to 0.7 percent. Of note, the incidence of drug-related events with lixisenatide in the clinical trials appears consistent with the other GLP-1 agonists. However, given the small numbers of events across all of the publications, it may be more instructive to look at the 95 percent confidence intervals rather than the incidence estimates.

These intervals demonstrate considerable overlap across the marketed class and with lixisenatide, despite the stimulated reporting of these events within the Sanofi program and the underreporting of events that may occur in the referenced voluntary post-marketing reporting systems. In total, these findings suggest that the risk for anaphylaxis with lixisenatide likely lies within the overall range observed within the class.

In summary, data from the clinical trials has identified a potential for allergic reactions in patients treated with lixisenatide and iGlarLixi. As these are peptides, this finding is not unexpected. To better characterize the nature of these reactions, Sanofi enhanced the reporting of all potential cases through the use of an events of special interest designation and added an independent adjudication committee.

This rigorous evaluation has revealed an incidence for severe allergic reactions that is very low, manageable, and appears consistent with reported risks for other GLP-1 agonists. Nevertheless, severe allergic reactions remain an important concern to us, which merit further characterization. And we are looking forward to working with the agency to establish a rigorous surveillance program focused on further evaluating this potential risk imbalance.

Finally, I would like to briefly discuss ELIXA, our large cardiovascular outcomes trial. ELIXA was a one-to-one randomized, double-blind,

placebo-controlled, event-driven trial designed to demonstrate cardiovascular safety with lixisenatide in a high-risk type 2 diabetes population. The patients enrolled in ELIXA had all experienced a documented ACS event within the 180 days prior to enrollment.

Sanofi focused on this high-risk population rather than a population of all comers with diabetes to be able to sensitively detect any risk in this subpopulation of greatest interest who might be treated with lixisenatide and iGlarLixi. Of note, in this safety study, additional glycemic therapy was left to the investigator's judgment and could be modified over the course of the study.

The primary analysis was a Cox proportional hazards model in the ITT population. The primary endpoint was time to first occurrence of a composite MACE-plus event as defined here to include cardiovascular death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina.

The secondary endpoints were defined as time

to first occurrence of any of the primary endpoint events, hospitalization for heart failure, or coronary revascularization procedure. The confirmed efficacy endpoints were those events that were positively adjudicated by the independent cardiovascular events adjudication committee.

ELIXA confirmed the cardiovascular safety of lixisenatide in this very high-risk post-ACS population. A measure of this cardiovascular risk can be seen in the notably high cumulative event incidence of approximately 13 percent at the median follow-up period of 25 months.

Additionally, the Kaplan-Meier curves for time to event occurrence for lixisenatide and placebo were superimposed over the duration of the study period, suggesting the absence of an adverse cardiovascular effect in either the immediate post-ACS period or with longer duration treatment.

The event rates for the composite secondary endpoints were also comparable between treatments, as were the individual components for the primary and secondary endpoints. All analyses showed

hazard ratios approximating 1. Of note, no increased risk of hospitalization for heart failure was observed with lixisenatide in this high risk population.

While the safety of the products has been rigorously evaluated in the combined programs, we recognize that new safety concerns can arise when products become available to much larger populations.

For this reason, Sanofi has prepared a post-marketing risk management plan for the U.S., which builds upon the foundation of activities currently in existence for lixisenatide outside of the U.S. and which is based upon the dual pillars of risk communication and risk characterization.

For clinicians and pharmacists, the primary vehicle for risk communication remains the U.S. prescribing information. Other supports available to physicians will include product training materials and medical device training to support physicians in the training of their patients on the proper use of these products.

For patients, in addition to the instructions for use, Sanofi will distribute a medication guide with each pen dispensed. These documents will outline important risks that patients should be aware of and will provide clear instructions on how to dial up the correct dose and how to inject the medication.

In addition, Sanofi will offer a patient support program. This program, administered by clinical nurse educators, will provide injection training, product information, and general assistance to support their overall diabetes management.

Finally, given the limited data available across the GLP-1 class for the rare event of anaphylaxis, Sanofi will perform a pharmacoepidemiology study using large healthcare data sources to further evaluate the incidence of anaphylaxis in the real world setting.

In conclusion, the data from the combined lixisenatide and iGlarLixi programs reveal a well-characterized safety profile that is built

upon the large development program for lixisenatide and, for iGlarLixi, the established safety of Lantus.

These programs demonstrated a safety profile that is comparable to other members of the GLP-1 class with respect to both general safety parameters and class effects of interest. Specifically, mild to moderate and transient GI complaints, a recognized class effect, were the most prominent adverse events and were lessened with iGlarLixi. And a generally limited and manageable risk for hypoglycemia was observed.

Rare instances of clinically severe anaphylaxis were observed in this program, which appear in the range observed with the marketed GLP-1 class.

Finally, as shown in ELIXA, no increase in cardiovascular risk was observed with lixisenatide in the very high-risk post-ACS population. The risks identified in our clinical development program can be appropriately managed with close post-marketing surveillance and the proposed risk

management plan.

Thank you for your attention. I will now turn the lectern over to Dr. Belder.

Applicant Presentation - Rene Belder

DR. BELDER: Thank you, Dr. Sharma. Good morning. I'm Rene Belder, and I'm the global project head for development of iGlarLixi and lixisenatide.

In my presentation, I will address the key issues raised by the FDA and provide data that support the approval and use of iGlarLixi. Specifically, I will discuss the contribution of lixisenatide to the overall effect of the combination across the entire dose range, then the effectiveness of the Lantus titration algorithm, and dose cap.

I will discuss the effects of the dose decrease that can occur upon initiation of iGlarLixi after switching from insulin or transitioning from pen A to pen B. Lastly, I will discuss how iGlarLixi, using either pen A or pen B, can be safely self-administered using the two easy

to recognize SoloSTAR pens.

Starting with the contribution of lixisenatide to iGlarLixi across the entire dose range, insulin requirements vary among patients with diabetes, and therefore a broad range of insulin doses was used across the studies. Thus, we wanted to assess the contribution of lixisenatide across the dose range.

Because iGlarLixi is titrated according to patient needs, it was not feasible to randomly assign patients into pre-defined, fixed-dose insulin groups. Thus, we analyzed the data based on the end-of-study insulin doses.

We looked at effects on A1c as the overall measure of clinical efficacy and the effect of lixisenatide on PPG excursions. We also looked at the weight gain mitigation across the entire dose range. Here we see the distribution across the end-of-study dose categories for both iGlarLixi and Lantus. To make it clear, in study 404, all patients started with the 10-unit dose, which was titrated based on patient's needs.

For this table, we determined for each patient what dose of insulin they were taking at the end of the study. In this table, we can see that 58 patients in the iGlarLixi arm were using a dose of insulin less than 20 units.

In these patients, it corresponded with a dose between 5 and 10 micrograms of lixisenatide. The majority of patients were on a dose between 20 and 60 units of insulin. In the iGlarLixi arm, this corresponded with a dose between 10 and 20 micrograms of lixisenatide.

Because only in study 404 we had patients in the lowest dose category, we are showing you the results of study 404. So let's first look at the hemoglobin A1c results across the dose range. iGlarLixi showed superiority over Lantus and lixisenatide, demonstrating a positive contribution of both components to the overall treatment effect.

When we now look at the treatment effect across the end of study insulin dose categories, we see effects in each of these dose categories that is consistent with the overall effect. This is

suggestive of a contribution of the lixisenatide component across the entire dose range.

In order to demonstrate this more clearly, we looked at the effects on PPG. The results of the iGlarLixi arm showed the lixisenatide effect on PPG across the entire dose range consistent with the effects of gastric emptying and PPG that were presented earlier by Dr. Newton, while in the Lantus arm we see no effect on the PPG.

Finally, we examined whether lixisenatide's beneficial effects on weight can be detected across the entire dose range. When we look at the changes in weight, in the iGlarLixi arm, we see weight reductions at the lower doses and an increase at the highest dose.

Contrary, in the Lantus arm, we see weight gain at all but the lowest dose, supporting a conclusion that lixisenatide contributes to the mitigation of weight gain across the entire dose range. Collectively, these data supports that the complementary effects of lixisenatide and Lantus provide clinically meaningful benefits to patients

across the entire dose range.

Because the phase 3 studies were open label, we looked at insulin doses over time to confirm the glycemic efficacy results were not affected by differences in titration between iGlarLixi and Lantus, or the choice of the titration regimen itself that limited patients on Lantus to a 60-unit top dose.

The titration algorithm for studies 404 and 405 aim to achieve a target fasting SMPG value between 80 and 100 milligrams per deciliter. Titration was to occur weekly. If the median fasting SMPG level from the previous 3 days was between 100 and 140 milligrams per deciliter, the insulin dose was to be increased with 2 units and, if the median was above 140, by 4 units. The investigators could use clinical judgment while making titration decisions. In both arms, patients were not able to exceed a dose of 60 units of Lantus.

This figure displays the mean daily insulin dose over time for study 404. We can see that the

insulin doses are gradually increased and are identical between the iGlarLixi and Lantus groups. Knowing that there was a negligible contribution of lixisenatide on FPG, we must therefore conclude that the titration algorithm was equally applied to both treatment groups.

These results suggest that the differences in glycemic efficacy between iGlarLixi and Lantus can be attributed to the complementary effects of lixisenatide on Lantus and are not due to differences in titration.

The effectiveness of the titration algorithm is displayed on the next slide. Between 40 and 45 percent of patients were able to achieve the fasting SMPG goal between 80 and 100 milligrams per deciliter. This was similar between the iGlarLixi and Lantus groups.

We see similar numbers when we look at FPG targets. However, investigators were able to use medical judgment when making titration decisions. And when we look at an FPG cut-off of 130, as proposed by ADA, we see a much higher percentage of

patients reaching this level, up to 79 percent.

It should be noted that the percentage of patients achieving A1c targets is higher with iGlarLixi, reflective of the contribution of lixisenatide on post-prandial glucose levels. To further assess the effect of the titration algorithm and the dose capping of Lantus, we performed simulations for study 405 using data from Lantus where the dose was not capped and where a different, more progressive titration algorithm was used.

This slide shows the change from baseline in A1c over time. The top line in black shows the observed results of study 405 for the Lantus arm. The bottom line in light blue shows the observed results for the iGlarLixi arm. The green and orange lines are simulated data under conditions where a more progressive titration algorithm was applied and the dose of Lantus was not capped.

This data shows that the titration algorithm or the dose capping did not have a material impact on the glycemic efficacy in the Lantus arm. The

apparent lack of a dose response at higher doses of Lantus was recently described by meta-analysis in almost 3,000 patients from 15 trials. The study compared changes in A1c in patients on doses below 0.5 or 0.7 units per kilogram in the blue bars, with dose in patients who exceeded these cut-off levels in the open bars. As indicated in this slide, patients on the higher doses did not have better responses in A1c.

These results support the ADA recommendation of considering other therapies than increasing the basal insulin dose once a dose higher than 0.5 units per kilogram has been reached. In fact, in study 405 the average dose of the patients on 60 units was 0.66 units per kilogram.

U.S. survey data among patients using Lantus from 2012 through 2014 shows that, indeed, only a minority of patients are prescribed doses higher than 60 units of Lantus, supporting the utility of iGlarLixi for a significant population requiring both therapies.

Some patients will experience a dose

decrease because of being on or being switched to iGlarLixi. This dose decrease can be a decrease in the dose of insulin in case of being switched from a basal insulin to iGlarLixi or a decrease in the dose of lixisenatide when transitioning from pen A to pen B.

So let's first look at the impact of the dose decrease in insulin. This graph shows the insulin doses over time in study 405. Insulin titration started during the lead-in period. However, in the iGlarLixi arm, patients who at the time of randomization were at an insulin dose of more than 30 units had to start at a 30-unit dose in order not to exceed the 10-microgram starting dose of lixisenatide.

As you can see, the insulin dose in the iGlarLixi group dropped at randomization and then caught up with the Lantus group over a 12-week period. And during the second half of the study, insulin doses were identical between the iGlarLixi and Lantus arms. The fact that the insulin doses are the same is expected since the titration

algorithm is based on fasting SMPG values and lixisenatide does not contribute to the change in dose levels.

When we look at the fasting plasma glucose levels over time we see that these are indeed higher in the iGlarLixi group at week 4. But by week 8, the iGlarLixi patients following the titration algorithm have achieved a similar fasting plasma glucose level as the Lantus arm.

When we look at the effect on A1c over time, we see that, at week 8, the iGlarLixi group is already doing better than the Lantus group, suggesting that the lixisenatide's effect on PPG levels counteracted the insulin dose decrease. This is because the 10-microgram dose of lixisenatide provides close to the maximal effect in post-prandial glucose levels. This is important when we investigate the effects of the lixisenatide dose decrease when transitioning pens.

When patients reach the top dose of pen A of 40 units of Lantus combined with 20 micrograms of lixisenatide, they can transition to pen B if they

require additional basal insulin. So for instance, if they titrate up to 42 units of insulin, which is only possible by transitioning to pen B, they will now receive 14 micrograms of lixisenatide. Let's see how that affects the glycemic control.

In this slide, we see the average A1c levels measured at 2 visits before and 2 visits after patients transition from pen A to pen B. The data shows that patients continue to improve their glycemic control with respect to hemoglobin A1c. In this case, the continuation of insulin titration has overwhelmed the effect of a small dose decrease of lixisenatide.

Finally, a couple of words about why we are confident that patients will be able to safely and appropriately use iGlarLixi to help them achieve their glycemic targets. The two fixed ratios of Lantus and lixisenatide provided in 2 SoloSTAR pens cover the needs of a broad range of patients. The 2:1 ratio provides a low starting dose for insulin-naïve patients combined with a clinically effective dose of lixisenatide. And at the top, a

combination of 40 units of Lantus with a 20-microgram dose of lixisenatide is adequate for most patients.

The 3 to 1 ratio provides a 30-unit and a 10-microgram dose for those patients switching from a higher dose of basal insulin. This ratio also covers the needs for patients all the way up to 60 units of Lantus combined with 20 micrograms of lixisenatide.

Sanofi has extensive experience with the SoloSTAR pen. It has been widely and successfully used in the United States for many years. There were few pen-related events using the SoloSTAR devices in the iGlarLixi clinical program, which was similar across treatment groups. Events that were related to the iGlarLixi pens were where patients injected doses outside the intended dose range.

Overall, 17 patients reported 22 events with iGlarLixi across both studies that were specific to the iGlarLixi pens. These numbers represent about 2 percent of all iGlarLixi patients and about

0.02 percent of all the injections. Importantly, there were no associated clinical events.

Even though the pen and instructions were successfully used in the clinical trials, some areas were identified to make further improvements for commercial use. With respect to the design of the pen, these were mechanical stops to avoid patients being able to dial to a higher dose than the intended dose. And reverse printing below the intended dose range to help patients identify the intended dose range.

We did not implement a low-end mechanical stop because patients want the opportunity to use remaining drug and supplement with another pen rather than discarding. The device design for the iGlarLixi pen is similar to the current commercial insulin pens that provide the option to use the remaining product in the pen.

Unlike in the clinical trial setting, kits will only contain one type of pen. And with respect to instructions, instructions will indicate a pen is for single daily injections. Instructions

will also indicate to discard the pen if the patient receives a prescription for a different pen.

Human factor studies validated that the pens can be used correctly. The results of the human factor study, including patients, nurses and pharmacists, demonstrated that the final design and instructions for use that were implemented in the commercial product are effective to support safe and appropriate use.

Participants were able to choose the pen among many pens, including competitor pens. They were able to choose the correct dose range and dial and administer the correct dose. They understood how to transition between the pens if they needed to do so and were also able to store the pen properly. In addition, an extensive patient education and support program will support the launch of the product once approved.

Given the fact that the overall success rate of the use of the device in the trial was similar between iGlarLixi and Lantus and given our

extensive experience with the Lantus SoloSTAR device, we are confident that the use of iGlarLixi will be safe and appropriate once launched. Additionally, at the request of the FDA, we will have the pens available during the lunch break for the advisory panelists to see.

I would now like to summarize the main points of my presentation. Lixisenatide contributes to the glycemic efficacy and mitigation of weight gain across the entire dose range. The treatment effects in study 404 and 405 are robust, are not influenced by the capping of the insulin dose, and are independent of the titration algorithm which was applied equally to both treatment groups.

The dose decrease in insulin or lixisenatide, when either switching from a basal insulin to iGlarLixi or transitioning from pen A to pen B, does not have an adverse impact on the glycemic control of the patients.

Finally, we are confident that patients will be able to safely and appropriately self-administer

iGlarLixi via once-daily subcutaneous injection offering both fasting and post-prandial glycemic control. Thank you for your attention, and I will turn the lectern over to Dr. Meneghini.

Applicant Presentation - Luigi Meneghini

DR. MENEGHINI: Good morning. My name is Luigi Meneghini, and I've been in academic medicine and clinical practice for over 23 years. I am currently a professor of internal medicine in the Division of Endocrinology at UT Southwestern Medical Center.

My deep personal and professional interest in, and relationship with diabetes, and the patients that struggle daily through this exhausting disease have shaped my clinical perspective on the treatment options presented here today.

The next few minutes I hope to convince you, if you're not already convinced, that the options presented will finally advance the treatment paradigm for how we approach injectable therapy in type 2 diabetes.

As Dr. Skolnik mentioned, almost half of patients on OADs have an A1c above 7 percent. And by the time we start insulin treatment in many of these patients, their average A1c has risen to around 9 percent or higher.

So what do we do? We start them on basal insulin, we actively titrate up their dose to correct their fasting hypoglycemia, and under the best of circumstances get about half of them to the desired A1c goal. We need to do better.

Unfortunately, in many cases, it takes years to effectively correct both fasting and post-prandial glucose and get the A1c to target. The astute clinician will hopefully turn their attention to correcting post-prandial hyperglycemia by adding a rapid-acting insulin before one or more meals, or switching patients to premix insulin, or by adding a GLP-1 agonist.

But as Dr. Skolnik points out, the transition from needing insulin to adequately replacing fasting and later post-prandial needs is too often painstaking and drawn out, leaving

patients like Betty, the patients we all see every day, exposed to unnecessary and damaging hyperglycemia for years.

Lixisenatide does provide another GLP-1 agonist option that specifically lowers post-prandial glucose. As you've seen, this becomes important for patients on oral agents who are more or less within 1 percent of their A1c goal, as well as for patients who are on appropriate amounts of basal insulin but whose A1c is still not at target.

Since lixisenatide provides a complementary mechanism to therapies that address fasting plasma glucose, it becomes a really attractive alternative to prandial insulin initiation, especially since it requires no carb counting, no frequent glucose monitoring, no dose adjustments, and can achieve similar control with less hypoglycemia or weight gain. Like other GLP-1 agonists, lixisenatide carries a low risk of hypoglycemia and is associated with weight loss. The GI side effects are also comparable to other preparations.

But let me get back to iGlarLixi because, if we need to start replacing insulin, why wouldn't patients like Betty and clinicians like Dr. Skolnik and myself, want a treatment that was simple with fewer injections, more effective at getting blood glucose under control by correcting all contributors to hyperglycemia, with no weight gain?

The data show a low risk of hypoglycemia of iGlarLixi that's comparable to Lantus and with improved GI tolerability compared to lixisenatide monotherapy. From a clinical, practical, and patient-centered perspective, this makes a whole lot of sense. In addition, this is a product that has established cardiovascular safety for both components.

I would also like to provide my perspective on two issues that have been raised, the use of pens and the risk of anaphylaxis. Firstly, I believe that the fixed-ratio combination will provide a dose range that will meet the need of most patients. Having the options of two SoloSTAR pens that provide a wide dosing range of up to 60

units, and two drug-to-drug ratios, will allow clinicians and their patients the flexibility to titrate iGlarLixi doses to balance therapeutic effectiveness with tolerability.

In addition, we all have had a tremendous experience with Lantus and with the SoloSTAR pen and can speak on how comfortable patients are using this technology. I do believe patients will have the same comfort level using iGlarLixi and, in addition, as you've heard, will have access to a robust patient support program.

Second, the risk of allergy and anaphylaxis presented in the data appears very low and comparable to other GLP-1 agonists. The risk management plan put forth by the sponsor appears reasonable and appropriate and will allow us to effectively utilize the benefits of iGlarLixi while minimizing any potential risks.

We have seen today that with iGlarLixi we can address both fasting and post-prandial glucose, allowing physicians to get to A1c target much more effectively with one single injection.

Looking back at the current recommendations, I see iGlarLixi fitting right into the treatment guidelines early on, when combination with oral therapy is no longer sufficient, and we need timely and robust A1c lowering or later when we need to intensify treatment beyond basal insulin replacement.

Overall, iGlarLixi is a needed and novel solution to the challenges that we face in type 2 diabetes. iGlarLixi is a new treatment option altogether, one that provides strong efficacy, robust safety, better tolerability, and a simplified practical treatment approach.

The clinical presentation that we've seen today provides convincing data that iGlarLixi will help healthcare professionals like Dr. Skolnik and myself provide more timely, more effective, more acceptable options for all patients with diabetes. Can we do better? Of course we can.

Thank you for your attention. I will now return the lectern to Dr. Chew.

DR. CHEW: Mr. Chairman, we're ready for

questions, clarifying questions.

Clarifying Questions to Applicant

DR. SMITH: I'd like to thank you all for the presentations, and we now have time for some clarifying questions from the panel members. Please focus on clarifying questions about the data and not topics we'll discuss later in regard to the discussion questions from the FDA.

If you would signal Commander Bonner on my left, I'll endeavor to get to everybody either now or in a later session today. I'd like to kick this off myself with a question that I think is probably directed to Dr. Sharma in regard to the allergic reactions.

The question is, if we consider the range of reactions from urticaria to anaphylactic reactions to full anaphylactic shock, can you provide any insight from the formal studies and from your other experience in Europe with the drug as to when the reactions occur on exposure, whether there are any predictors, whether there is a correlation with the presence or titer of anti-drug antibodies, prior

characteristics of patient history? Are there any ways that you can provide predictors or insights into that?

DR. CHEW: Dr. Sharma? I'd like to summarize the question. It's the relationship of allergic reactions to any drug antibodies post-marketing experience, any predictors.

DR. SHARMA: Certainly. If we begin with the post-marketing experience, we do have experience outside of the U.S. We have 41,000 patient-years of experience. What we've seen with respect to those allergic reactions are a profile that's really quite comparable to what we've seen in the trials. So most of the events that we're seeing are urticaria --

DR. SMITH: Yes, I don't really want to know about the percentage of events. What I want to know about is predictors in advance of the event based either on timing or on other patient characteristics.

DR. SHARMA: Okay. We've certainly looked at whether we could identify risk factors related

to the events. We looked at demographics, we looked at history. Really, the only risk factor that came out to us, in reviewing all the cases we've seen in our clinical trials, is a history of allergy, which would be expected for any type of a drug reaction.

We also looked at the anti-drug antibodies to see if we could see a relationship there and we did not. When we looked at the drug-related events in our phase 3 trials, the incidence of patients who were ADA positive and ADA negative were really balanced. So it didn't appear to represent a risk factor or a correlation to the event.

DR. SMITH: And how about the timing? Do they occur early specifically? Or you mentioned one first dose event. Do they occur after a long period of exposure?

DR. SHARMA: The events typically occur within the first several weeks after the exposure, although, as noted in the presentation that we gave, for example, in the 4 cases that we were looking at, two of them occurred after day 1 and

day 2. But typically, it's in the first couple of weeks of exposure.

DR. SMITH: So maybe you could provide some concrete sort of information on that maybe later today to actually show the distribution of that. I'm being specific because I'm trying to understand whether there would be some logic to a more intensified focus that might be given as advice to users or whether that would not be supported based on the distribution over time. So if you could pull that together a little bit and show us that that would be good.

DR. CHEW: Yes, after the break, we'll do it and, if I understand the question correctly, it's the timing.

DR. SMITH: That would be good. Thank you. Dr. Seely had a question.

DR. SEELY: I had actually two questions. So one thing we're talking about is approving lixisenatide alone. And most of the presentation was about the combination. So I was interested in, you've been marketing it in the EU since 2013. So

what does lixisenatide give us that the other GLP agonists don't give us that should make us approve it? That's one question.

The second question was that I was concerned that, if you look at slide 20 C0-54, the completion rates did not look similar between the two groups. And it looked like there was a twofold higher dropout, discontinuation, loss to follow-up, dropout -- it's not explained -- in the combination group. And I was interested in how that might affect the results.

So I guess this one is first. If you're going from 366 to 346, losing 20 subjects versus 385, 365 to 355 losing 10 subjects. So you're losing 20 versus 10. And I'd be interested in what happened to those 20. Were they lost to follow-up? Were they dropouts because of ineffectiveness? Were they dropouts because of side effects? And did it differ between the two groups? And how would your results look if you put those back in and do more of an intention to treat?

DR. CHEW: Dr. Meehyung Cho?

DR. CHO: Meehyung Cho, biostatistics. This slide shows the missing data in this study at week 30. As you see here, in both studies, the percentage of patients with missing HbA1c data at week 30 was very low, around 5 to 6 percent, actually less than 6 percent. They are generally similar. So pretty much, there's no real impact. But I'll show you the result from the sensitivity analysis shortly.

Actually, of these patients, of the 6 percent of patients, about 34 percent of them actually came back after treatment discontinuation and had their HbA1c data. And here shows the result for the primary and sensitivity analysis and this sensitivity analysis will include all MITT patients.

If you look at the bottom 3, PMM, those three-panel mixed models completed treatment versus non- or jumped to control for the missing data in the iGlarLixi arm and the multiple imputation using the random draws from the baseline HbA1c data for the missing data in the iGlarLixi arm. All models

show a very consistent result with the primary results.

DR. SEELY: Then why do we want lixisenatide alone to treat our patients?

DR. CHEW: Thank you. The most important distinguishing factor about lixisenatide compared to the other GLP agents is its strong effects on post-prandial glucose. Post-prandial glucose is at least 50 percent, sometimes 70 percent of the hyperglycemic burden.

In fact, the closer you get to goal, the more prominent it is. And lixisenatide has a significant effect on that component of hyperglycemic burden. And not only that, the lixisenatide program has shown effectiveness in reducing A1c across a range of therapies.

DR. SEELY: No, I know that. In terms of showing data comparing lixisenatide compared to currently available GLP agonists, in terms of its superiority, you didn't present that data and that would be helpful to see.

DR. CHEW: We haven't performed superiority

studies across them, but the important point to note is that patients, as they try to get glycemic control, need better post-prandial glucose control, and that's one of the aspects of lixisenatide.

DR. SEELY: Right. But is that post-prandial glucose control not achievable with a different GLP-1 agonist?

DR. CHEW: While we haven't done comparative studies on that point, that is one aspect that distinguishes this product from the literature that we've seen.

DR. SMITH: Okay. Dr. Budnitz?

DR. BUDNITZ: Yes. You described the combination product delivery system pen. Can you tell us a little bit about the lixisenatide-only delivery device? Is it in a similar pen? Is it in a dial-able dose? How is that going to be delivered?

DR. CHEW: The lixisenatide-alone pen is going to be 2 fixed-dose pens. The first dose, the green pen, is 10 micrograms for 2 weeks, then up-titrated to the second pen, which is

20 micrograms. So they're sequential pens, and it's a fixed dose. It's not variable. You don't dial it. It's an injection.

DR. SMITH: Dr. Burman?

DR. BURMAN: Yes. Just a point of clarification. Although you're asking for proposed indication for uncontrolled diabetes, do you have any studies of patients who were on GLP-1 agonists and then you add on the combination or switch to the combination? You have patients who were on long-acting insulin and then started it, but I didn't see the other way around.

DR. CHEW: If I understand the question correctly, Dr. Burman, it is, do we have data on patients who need intensification beyond the GLP-1?

DR. BURMAN: Correct.

DR. CHEW: Yes, we don't have data on that. We're about to start a trial examining that specific question, but as of today, the answer would be no.

DR. SMITH: Dr. Meisel?

DR. MEISEL: Thank you. I've got a couple

of questions that sort of build on each other. First, would it be fair to conclude that lixisenatide is not insulin sparing, that the doses of insulin that are given would be about the same?

I'm looking at the slide 90 that you presented a short time ago and it seems like the dose of insulin that was final was about the same for both groups. And that implies to me that this is not an insulin-sparing approach, that it's an additive approach, let's add the lixi because glargine hasn't fully worked. Would that be a fair conclusion?

DR. CHEW: Well, your observation is correct. The reason we have the combination is that the insulin, Lantus, addresses fasting plasma glucose and lixisenatide does not. It addresses the post-prandial glucose. Since the titration of patients with Lantus or iGlarLixi is based on fasting self-monitored glucose, what you see is the identical titration in terms of the Lantus or the Lantus component.

DR. MEISEL: So that would then explain why

the hypoglycemia rates are about the same for both groups. So with that in mind, if I go back to slide 46, can you explain why lixi alone is more effective in that 2 hour PPG excursion than the combination is if the dose of glargine is the same for both groups?

Is it because in the combination, we end up giving less lixisenatide than we do when we do it alone?

DR. CHEW: On slide 46, on the right side of the PPG excursions, lixisenatide is administered as 20 micrograms and iGlarLixi is titrated.

DR. MEISEL: Right.

DR. CHEW: And I believe the titrated final dose of lixi component is about 15 micrograms in that particular study. So they're very similar, as you can see, in terms of the PPG excursion, but there's a little less lixi in the iGlarLixi arm.

DR. MEISEL: So by giving the same dose of insulin, we end up with less of the lixi, therefore a decreased effect on the 2-hour PPG excursion?

DR. CHEW: Well you still preserve a great

deal of it. And the important aspect is what we do see, and that's the A1c reduction with iGlarLixi versus lixi.

DR. MEISEL: Okay.

DR. CHEW: So you can see on 404, the 7.3 versus a 6.5. So the A1c is considerably enhanced with the iGlarLixi versus lixi alone.

DR. MEISEL: Okay. One additional question, and that is, as you know, although it's not labeled this way, Lantus is commonly given BID in the real world. So if that were to happen with this product, depending upon the dose, somebody gives 40 in the morning and 30 at night or something like that, we'd end up with an overdose of the lixi.

How would you propose preventing that sort of a situation from happening? If people perceive that Lantus needs to be given twice a day in some patients, and then we have a situation here where the dinnertime effect of the lixi is much weaker than it is for the breakfast time effect because of a short half-life, I could see that motivation to be driving this to a BID dosing schedule with an

inadvertent result of overdoing the lixi.

DR. CHEW: Yes, that's a question that's very important to us. We have a lot of experience on these pens. These pens will be distinguished by their color, their labeling, and the number in the dial. And it will be important also in our patient support, our training of physicians and pharmacists to ensure that the iGlarLixi pens are safely used.

Dr. Meneghini, do you have comments on that?

DR. MENEGHINI: Yes, I do. While I think that the BID Lantus dosing is a more common practice in type 1 diabetes, it's not needed in type 2 diabetes unless doses exceed a certain range. And as you've heard, there is a certain dose limitation up to 60 units, and so I don't see that as much of an issue in clinical practice specifically for the treatment of those patients with type 2 diabetes.

DR. MEISEL: But is iGlarLixi the proposed generic name of this?

DR. CHEW: That will be the generic name, correct.

DR. MEISEL: Thank you.

DR. SMITH: Dr. Neaton?

DR. NEATON: Yes, thank you. I'm just curious, when you tried to understand the dose of insulin on hemoglobin A1c responses, why you chose not to look at study 405 because there you had roughly half the people that used pen A and pen B as I understood it, or above and below 40. Why didn't you use that data? That at least is protected by randomization.

You say in the report, for the slide you showed, that comparisons are invalid, so it's kind of hard to know what to make of it.

DR. CHEW: Dr. Belder?

DR. BELDER: So I'm afraid that I don't understand your question correctly.

DR. NEATON: You showed us slide 90. In your report, you made the comment, which I would agree with, that this is not protected by randomization and any statistical comparison is invalid. And so you also said that you didn't do this in study 405 and it just seemed like you had a

comparison there that was a natural one to consider that was protected by randomization.

So can you show us data from 405 for what the hemoglobin A1c response was for people who came in with a dose of insulin less than 40 versus greater than 40?

DR. BELDER: I don't think that I have the data. So we did do this same analysis in study 405 as well.

DR. NEATON: I would agree with that one. That one would be equally invalid in my mind.

DR. BELDER: Yes, exactly.

DR. NEATON: But I think what I guess I would like to see is the comparison.

DR. BELDER: But I'm just thinking in my mind how it would work because patients -- although obviously they switch to -- let us think about it, and then let me see.

DR. NEATON: And I guess the second question is, is that --

DR. SMITH: So just for a moment, if there's an opportunity to come up with those data later

today, we'd appreciate you doing that --

DR. BELDER: Sure. Yes.

DR. SMITH: -- or however you can approximate that.

DR. CHEW: Let's just make sure I understand the question. The question is looking at study 405 and looking at the subgroup analysis by your final dose.

DR. NEATON: Looking at the subgroup analysis by initial dose of insulin.

DR. CHEW: With the initial dose, yes. Yes, the initial dose.

DR. NEATON: Yes, the initial dose of insulin. And then also in study 405, the hypoglycemia percentages seem similar. There's a modest difference in weight. I couldn't find in the report or in your presentation what is the impact of the combination on nausea and GI effects. You've pooled the data, but in that population that we're going to be asked to consider later, separately, what's the rate of nausea and GI, major GI side effects in the two groups?

DR. CHEW: So this would be the GI side effects of iGlarLixi in both 405 and 404.

Dr. Sharma?

DR. NEATON: I mean, I saw the pooled data, I'm interested in just 405.

DR. CHEW: Oh, 405. Okay.

DR. SHARMA: Okay, so the slide here presents the difference in the GI events from study 404 and from 405. And if you look across that row 3, in the iGlarLixi arms, you see that the GI events are a bit lower in 405.

DR. NEATON: Yes, so basically though, what I'm interested in here is, I look at GI disorders and so an interpretation of this perhaps would be that hypoglycemia is kind of a wash. It's pretty similar between the two groups, perhaps slightly less in the combination, although more severe events with the combination. Weight is modestly different, but GI effects are greater. We agree?

DR. CHEW: I'm sorry, the GI side effects of iGlarLixi?

DR. NEATON: Are higher --

DR. CHEW: Compared to lixi alone.

DR. NEATON: -- compared to insulin in 405.

DR. CHEW: Yes.

DR. NEATON: I'm trying to understand the risk-benefit in this target population that you came in with insulin and now you're going to decide whether to switch them to a combination product.

DR. CHEW: There were fewer GI side effects compared to lixisenatide, but more seen with iGlarLixi --

DR. NEATON: No. I know.

DR. CHEW: -- than with Lantus alone, yes.

DR. NEATON: Okay. If I can ask one last question related to safety, you did a nice cardiovascular outcomes study. It looks like it's overall not much difference. At the end of the study or on treatment, in one of the tables you had, roughly 50 percent of them were taking insulin. Do you have a subgroup analysis according to whether people were taking insulin at entry for that study? You've presented a lot of other subgroup analyses.

DR. CHEW: Yes, we do. What we did here is to look at ELIXA patients who were randomized to lixisenatide or placebo and whether they were on insulin at baseline, yes/no. So what you see here is the overall MACE plus the primary event was very similar to the 1.02, I believe, for the primary.

DR. NEATON: Thank you.

DR. CHEW: Yes.

DR. SMITH: Dr. Yanovski?

DR. YANOVSKI: Dr. Burman already asked my question. Thank you.

DR. SMITH: And Dr. Wilson?

DR. WILSON: So I was wondering about the time of the day of the injection -- I don't think I heard about that -- and also the time of day for mixed meals or glucose challenges because you keep coming back to the post-prandial effects. Does it hold, for instance, if you took your injection in the morning, if you had a mixed-meal challenge at midday or later in the day? I think all us metabolic scientists would like to know that result.

DR. CHEW: Dr. Newton?

DR. NEWTON: So I'm going to start with a clinical pharmacology study where we looked at the effect over the day of a single 20-microgram dose with standardized meals in each situation. And you can see that there's a reduction in AUC for post-prandial glucose over all three meals, but certainly the most profound effect is after injection.

Actually, it differs a little bit. After the first meal, you get a significant reduction in the maximal amounts, where at lunch and dinner it tends to be more evenly distributed over the AUC as far as the effect goes.

DR. WILSON: I'll follow up with that. I could see I might have to think about this, and have a patient in front of me, and say, it might make the most sense to take this before the biggest meal. I'm sure you've thought about this, too, but you don't have data on that yet. Is that fair to say?

DR. CHEW: Our recommendation will be to

take this in the morning before breakfast or the big meal of the day.

DR. SMITH: Okay. So I know there are a few panel members with more questions. We'll have an opportunity to come back to those later today, but we need to take a break. So we're going to take a break until 10:30. That's a 12-minute break. I'm shortening it a little bit.

Panel members, please remember there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. So we'll resume at 10:30.

(Whereupon, at 10:18 a.m., a recess was taken.)

DR. SMITH: So I'd like to welcome everyone back, and we're now going to proceed with the FDA presentations and I think that is started off by Dr. Balakrishnan.

FDA Presentation - Suchitra Balakrishnan

DR. BALAKRISHNAN: Good morning. My name is Suchitra Balakrishnan. I'm a medical officer in the Division of Metabolism and Endocrinology

Products. On behalf of the FDA review team, I would like to thank the committee for being here today.

Today, we will be presenting the FDA findings from the review of the GLP-1 receptor agonist lixisenatide and the fixed-ratio combination product of insulin glargine and lixisenatide.

I will start with an introduction to lixisenatide. I will then briefly summarize the efficacy of lixisenatide followed by a discussion of the safety findings from the development program, focusing on non-cardiovascular safety. Dr. Yueqin Zhao will then present the results of the cardiovascular outcome study, ELIXA.

After presenting the information for lixisenatide, we will move on to FDA's findings for the fixed-ratio combination product. I will briefly discuss the proposed fixed-ratio combination drug product. This will be followed by a discussion of efficacy by Dr. Jiewi He.

I will then discuss some of the secondary

endpoints, the safety findings, and additional clinical considerations with regard to this product. Dr. Ariane Conrad will then discuss the findings from the human factors study. I will end the FDA presentation with a summary of both clinical programs.

Lixisenatide is a member of the GLP-1 receptor agonist class of drugs. This will be the sixth approved member of the class, which includes drugs dosed twice daily, once daily, and 3 drugs dosed once weekly. It is a synthetic amino 44-amino-acid peptide with a modified C-terminal to resist degradation by dipeptidyl peptidase IV.

It has structural similarities to exenatide and exendin-4 and a high degree of homology to endogenous GLP-1 and glucagon. Through agonism of the GLP-1 receptor, lixisenatide potentiates glucose-dependent insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

Pharmacokinetic studies for lixisenatide demonstrate a time to maximum concentration of 1 to 3.5 hours in patients with type 2 diabetes. The

apparent terminal half-life after multiple doses is approximately 3 to 4 hours. The presence of anti-drug antibodies increased overall exposure as well as the variability in the right PK parameters. Elimination half-life is increased to around 8 to 10 hours in the presence of antibodies.

The dose response curve generated by the applicant based on data from the phase 2 dose finding study is shown. The estimated ED50 was 11.4 micrograms. Placebo adjusted change in HbA1c was minus 0.31 percent for the 10-microgram once-daily dose and minus 0.5 percent for the 20-microgram once-daily dose.

In the phase 2 dose-finding study, the applicant studied a once-daily and a twice-daily dosing regimen. Though the twice-daily regimen resulted in numerically greater reduction in HbA1c and fewer gastrointestinal events, the applicant opted to study a once-daily regimen in phase 3 and to study only a 20-microgram dose.

Additionally, the applicant utilized two approaches to dose titration. In the 1-step

titration, a dose of 10 micrograms was administered once daily for 2 weeks and then the dose was increased to 20 micrograms. In the 2-step titration, a dose of 10 micrograms was administered once daily for 1 week, increased to 15 micrograms for 1 week, and then increased to 20 micrograms.

Both titration schemes were studied in two of the phase 3 studies. In those studies, the 1-step titration resulted in numerically greater reduction in HbA1c, though the difference between the treatment groups was small. There was also a lower incidence of nausea and vomiting with 1-step titration compared to 2-step titration.

Based on the clinical studies, the applicant is proposing a once-daily subcutaneous injection for lixisenatide. Dosing will start with the 10-microgram dose that will be administered for 14 days, followed by an increase to the therapeutic dose of 20 micrograms.

This is the second time that the FDA is reviewing lixisenatide. Lixisenatide was previously submitted for review in December 2012.

Prior to the action date, the NDA was withdrawn. Lixisenatide was submitted again in July 2015 following completion of ELIXA, the cardiovascular outcomes trial.

I will now discuss the efficacy findings for lixisenatide. The phase 3 studies considered by the FDA as pivotal to support lixisenatide were randomized, double-blind, placebo controlled studies. The primary endpoint was change from baseline to HbA1c, and this was generally assessed at 24 weeks.

The FDA has generally requested that new anti-diabetic drugs be studied in placebo-controlled studies using certain clinical settings. These are, as monotherapy, as add-on to metformin, as add-on to sulfonylurea, and as add-on to insulin. These are requested to characterize the efficacy and safety in these clinical settings.

In addition to these studies, many applicants perform other studies, including active control studies. The discussion of efficacy will be limited to findings for change in HbA1c.

In the placebo-controlled phase 3 studies, lixisenatide demonstrated a greater reduction in HbA1c compared to placebo. Studies considered to be pivotal to the FDA are shown here. The analysis shown is a mixed-effect model with repeated measures or MMRM analysis using all available post-baseline observations regardless of treatment discontinuation or initiation of rescue therapy.

The applicant also performed several active control studies. In the study comparing lixisenatide to exenatide BID, lixisenatide was statistically inferior. In the study comparing lixisenatide to insulin glulisine, lixisenatide was non-inferior to insulin glulisine once daily, and was statistically inferior to insulin glulisine 3 times per day.

EFC10780 compared lixisenatide to sitagliptin. The primary endpoint was not HbA1c change from baseline. There was no statistically significant difference for change in HbA1c on comparing lixisenatide to sitagliptin. The primary endpoint was a percentage of patients with HbA1c

less than 7 percent and a weight loss of 5 percent or more. No statistically significant difference was seen for the primary endpoint.

Some of the phase 3 studies had up to 16 percent of missing data. Sensitivity analysis using multiple imputations for missing values confirmed the conclusions from the MMRM analysis.

The exception was study EFC12626, the study comparing lixisenatide to insulin glulisine. The sensitivity analysis for this study did not exclude the prespecified non-inferiority margin of 0.4 percent for lixisenatide compared to insulin glulisine 3 times per day.

I will now discuss safety issues for lixisenatide. The overall safety population for lixisenatide included a pool of placebo-controlled phase 3 studies with 2,869 subjects treated with lixisenatide with a total of 3,282 patient years.

In the pool of phase 2 and phase 3 studies, there were 7,874 subjects treated with lixisenatide and a total of over 10,000 patient-years of exposure. Over half of this exposure came from the

cardiovascular outcomes study, ELIXA.

I will be focusing on the comparison to placebo for my discussion of safety. There was no evidence of an increased risk of death with lixisenatide. Most of the phase 3 studies had deaths adjudicated into three categories and this observation held true across all three categories. Most of the deaths occurred in ELIXA.

In the phase 3 placebo-controlled studies, the incidence of serious treatment emergent adverse events was generally similar in both treatment groups, 8.5 percent with lixisenatide and 7.8 percent with placebo. This was also true for the ELIXA study. Major cardiovascular events are not included in this calculation.

Subjects treated with lixisenatide were also more likely to discontinue due to an adverse event. Consistent with the GLP-1 receptor agonist class, the most common cause of discontinuation was nausea and vomiting.

GLP-1 receptor agonists carry concerns for gastrointestinal events, hypoglycemia,

pancreatitis, thyroid C-cell hyperplasia, renal failure secondary to volume depletion, and hypersensitivity reactions. I will not be covering those safety concerns, as the finding for the lixisenatide development program are generally consistent with other GLP-1 agonists.

For a safety discussion of lixisenatide I will focus on immunogenicity and hypersensitivity reactions due to a signal for anaphylaxis seen in the lixisenatide development program.

Exposure to lixisenatide resulted in the development of anti-drug antibodies. The incidence of positive anti-drug antibodies status increased over time and plateaued at approximately 70 percent at 24 weeks.

Acknowledging that the assessment of the rate of anti-drug antibody development is highly dependent on several factors, which include assay methodology, timing of the sample, and underlying disease, it is notable that the incidence of anti-drug antibodies is higher than that reported with the approved GLP-1 agonists.

In addition to an increased instance of positive anti-drug antibodies, the concentrations of these antibodies increased over time. Forty-four percent of lixisenatide-treated subjects had measurable concentrations of antibodies at 76 weeks.

Lixisenatide shows a high degree of amino acid homology with the first 12 amino acids of endogenous GLP-1 and glucagon. Therefore, it is possible that antibodies to lixisenatide could cross-react with endogenous GLP-1 and glucagon and influence glucose metabolism.

Cross-reactive antibody was assessed in three studies only. Of the 1,269 subjects tested, 28.4 percent tested positive for anti-drug antibodies cross-reacting with endogenous GLP-1. And 4.7 percent of subjects had anti-drug antibodies cross-reacting with glucagon. Antibodies that would neutralize the effect of lixisenatide were not evaluated in the development program. These types of antibodies may affect the efficacy response.

The concern with cross-reactive antibodies is the potential impact on safety and efficacy. If antibodies cross-react with endogenous proteins, this could block the activity of that protein. Antibodies that cross-react with endogenous GLP-1 could interfere with normal glucose homeostasis. And antibodies that cross-react with endogenous glucagon could increase the risk for hypoglycemia.

Additionally, if these antibodies persist despite discontinuing therapy, they could continue to cross-react and have an effect on the patient. Data on cross-reactive antibodies after discontinuation of therapy is not available.

The effect of antibodies on efficacy was assessed by exploratory subgroup analysis. At 24 weeks, there is a decline in the efficacy response that corresponds with an increasing antibody concentration.

Notably, those subjects with an antibody concentration over 100 nanomoles per liter did not have a statistically significant reduction in HbA1c, though the sample size is small. At

76 weeks, a similar trend was observed.

Acknowledging that these are subgroup findings from a small number of subjects, it seems to suggest that the presence of anti-drug antibodies, particularly at high concentrations, may adversely impact the efficacy of lixisenatide. This could be due to chance, but could also indicate the presence of neutralizing antibodies. As mentioned earlier, testing for neutralizing antibodies was not performed.

The presence of anti-drug antibodies appear to correlate with an increased incidence of adverse events. The incidence of adverse events in anti-drug antibody-positive subjects was increased overall. Adverse events more common included hypoglycemia and injection-site reactions. The incidence of injection-site reactions appeared to increase with increasing antibody concentrations. Gastrointestinal disorders overall, and nausea, and vomiting were not affected by antibody status.

The immunogenicity findings also raised concerns about increased risks for

hypersensitivity. I will now discuss hypersensitivity events in the lixisenatide program. The applicant established an allergic reaction adjudication committee.

For nearly all of the phase 2 and phase 3 studies, potential hypersensitivity events were reported on a specific adverse event form and were periodically sent to the ARAC.

The ARAC adjudicated the events into the categories shown here: urticaria, angioedema, anaphylactic reaction, anaphylactic shock, and others. The ARAC was also tasked with assessing whether the event appeared to be related to study drug.

As it would be hoped that these events would occur infrequently in a development program, I am presenting the actual number of cases rather than percentages. Recall that randomization for lixisenatide to placebo was 2 to 1. While there were more cases of urticaria and angioedema in the lixisenatide-treated subjects, the incidence for these events was generally similar.

For cases of anaphylaxis, which is considered a serious and life-threatening event, there appears to be an increased risk with lixisenatide compared to placebo.

When considering those events that were attributed to study drug, it is notable that none were reported with placebo. Though the overall incidence of anaphylaxis is low, it is unknown whether the findings from the lixisenatide development program will translate into an increased magnitude of risk for anaphylaxis in the post-marketing setting.

It is worth noting that a signal for hypersensitivity was not seen in the development program of the approved GLP-1 receptor agonists, and this concern was only identified in the post-marketing setting.

We acknowledge that there are differences between the lixisenatide development program and those of the other GLP-1 receptor agonists that could have contributed to the identification of this safety signal. The lixisenatide program is

larger than other GLP-1 receptor agonist programs, which may have resulted in more events occurring.

Additionally, events may have been better captured due to the adjudication. In considering the potential contribution of adjudication to identify events, we also considered whether a signal would have been seen using investigator-reported terms. Using the standardized MedDRA query for anaphylaxis, we still see a signal for anaphylaxis with lixisenatide.

Review of the individual cases suggest that the majority of cases identified in the lixisenatide program were likely due to the investigational medical product. One reflection of this is how many of these events led to discontinuation of study drug. Eleven of the 16 adjudicated anaphylaxis events in the lixisenatide arm led to treatment discontinuation versus none with placebo. Six of the 8 identified from investigated reported terms in the lixisenatide arm led to treatment discontinuation versus none with placebo.

Acknowledging the smaller size of the development programs, anaphylaxis seen with other approved GLP-1 agonists were attributed to other causes and did not lead to discontinuation of study therapy.

In summary, there is a signal for anaphylaxis and hypersensitivity, and the magnitude of risk in the post-marketing setting is unknown. While there are post-marketing data available with lixisenatide and approved GLP-1 agonists, there are serious limitations to this data.

Now Dr. Yueqin Zhao will discuss the findings from the cardiovascular outcomes study, ELIXA.

FDA Presentation - Yueqin Zhao

DR. ZHAO: Good morning. My name is Yueqin Zhao and I am a statistical reviewer from the Division of Biometric VII in the Office of Biostatistics. In this talk, I will present our evaluation of cardiovascular safety of lixisenatide using evidence from the completed cardiovascular outcome trial, ELIXA.

I will start with a brief review of the trial design and the statistical methods. This will be followed by a description of the trial population based on subjects' demographic and baseline characteristics. Next, I will summarize the results of subject disposition and exposure length. After that, the findings of MACE-plus, MACE, and all-cause mortality will be presented. This presentation will end with some summary points.

The objective of the ELIXA trial was to rule out a relative excess cardiovascular risk of 30 percent for lixisenatide versus placebo, where the 1.3 risk margin is in accordance with the 2008 FDA guidance on establishing cardiovascular safety of a new anti-diabetic product.

ELIXA was a double-blind, placebo-controlled, randomized, 2-arm, multinational, event driven, phase 3 clinical trial. Subjects were randomized in a 1:1 ratio to either lixisenatide or placebo treatment. For the enrollment of subjects into the trial, no

background anti-diabetic medications were specified. Subjects were eligible regardless of whether or not they were receiving pharmacologic treatment for type 2 diabetes mellitus.

During the double-blind treatment period, subjects in both treatment groups were allowed to continue lifestyle and diet therapy and take other anti-diabetic treatment except other GLP-1 receptor agonists or DPP-IV inhibitors.

The lixisenatide treatment in this trial consisted of one injection every day within 1 hour prior to breakfast. The starting dose for lixisenatide was 10 micrograms. This dose included a 1-step increase at 2 weeks to 20 micrograms, which was maintained throughout the trial or titrated based on subject tolerability.

ELIXA was based upon an enriched population for cardiovascular events. This included type 2 diabetes patients who were at least 30 years old with a baseline HbA1c between 6 percent and 10 percent.

The trial was designed to enroll subjects

who experienced a spontaneous acute coronary syndrome event within 180 days prior to the screening visit. Acute coronary syndrome is defined as a ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction or unstable angina.

Among other exclusion criteria, key exclusions were for subjects with a history of type 1 diabetes and having used other GLP-1 receptor agonist of DPP-4 inhibitors as the baseline.

In the ELIXA trial, the primary study endpoint was the time to first occurrence of MACE-plus, which included any of the following partly adjudicated events: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalizations for unstable angina.

Hospitalization for unstable angina is defined as an unplanned hospitalization for worsening angina with objective evidence of myocardial ischemia, but insufficient criteria for myocardial infarction.

In addition to the assessment of MACE-plus,

the applicant was requested to also investigate MACE, a composite endpoint defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. All-cause mortality was studied as a secondary endpoint. All the cardiovascular events were adjudicated by a committee of specialists blinded to treatment assignment.

Now I will discuss the statistical methodologies used in the ELIXA trial. The primary analysis population was the intent-to-treat population. This was defined as all randomized subjects who had a subject number and a treatment kit number allocated to them based on the randomization scheme.

Two censoring strategies were applied. The primary censoring strategy was on-study censoring. Using on-study censoring, cardiovascular events contributing to the analysis include those occurring from randomization to the common study end date, even if a subject discontinued randomized treatment.

As a sensitivity analysis, an on-treatment censoring strategy was applied. Such a censoring strategy included events that occurred from randomization up to 30 days after the last injection of randomized product.

As the evaluation of the 1.3 risk margin was planned to occur only at the trial completion, tests were conducted at the two-sided type 1 error rate of 0.05, which corresponds to a 95 percent confidence interval.

The applicant performed time-to-event analysis for cardiovascular and mortality endpoints. The analyses were performed using Cox proportional hazard model with treatment and region as the covariates. The hazard ratio between lixisenatide and placebo, and the associated two-sided 95 percent confidence intervals were estimated.

The trial objective, that is, ruling out a relative excess rate of 30 percent, would be considered to be met if the up-bound of the two-sided 95 percent confidence interval or the hazard

ratio is less than the 1.3 risk margin. The primary and secondary analysis were both based on the ITT population and analyzed with the Cox models, but applying on-study and on-treatment censoring respectively.

Now I will discuss the findings from the ELIXA trial. The table here shows the demographic, regional and baseline characteristics of subjects in the two treatment groups, all of which were balanced between the two groups. The mean age was around 60 years. More male and Caucasian subjects were enrolled in the study.

The majority of the subjects were either obese or overweight with a mean body mass index around 30 kilogram per square meter. Around 11 percent of subjects were from the United States. Around 11 percent were current smokers. Around 40 percent of subjects had durational diabetes over 10 years. And the mean baseline HbA1c was around 7.6 percent.

The table here shows that the baseline cardiovascular characteristics of subjects were

similar between the lixisenatide group and the placebo group. Around 13 percent of subjects has the qualifying ACS less than 30 days before randomization. Around 44 percent of qualifying ACS events were ST-segment elevation MI. Around 60 percent of subjects were categorized as New York Heart Association class 1 for heart failure risk. And over 90 percent of subjects were on statins at the baseline.

The table here shows as the background therapy at baseline in the lixisenatide group were comparable to those in the placebo group. The majority of subjects were on one or more pharmacologic treatments for diabetes and only around 6 percent of subjects were on diet and exercise only as the baseline.

The table here is a snapshot of the subject disposition. The intent-to-treat population included 6,068 subjects with 3,034 subjects randomized to the lixisenatide group, and 3,034 randomized to the placebo group.

A similar percent of subjects did not

complete the trial, 3.5 percent in the lixisenatide group and 3.6 percent in the placebo group, among which the majority of discontinuations were due to subject request, 2.9 in the lixisenatide group and 2.7 in the placebo group. The proportions of subjects with known vital status were similar between two groups with a known vital status of around 99 percent.

This plot shows the distribution of treatment exposure time for the ITT population for two groups, green corresponding to lixisenatide and blue corresponding to placebo. The median treatment exposure time was 679 days for the lixisenatide group and 701 days for the placebo group. The total patient-years of treatment exposure for lixisenatide and the placebo groups were 5,820.2 and 5,997.5 years respectively.

Next I will discuss the findings of the cardiovascular outcomes, including MACE-plus and MACE. Then I will briefly talk about the findings of all-cause mortality.

As a descriptive analysis, here, the

Kaplan-Meier curves of time from randomization to the first MACE plus event for lixisenatide and placebo was superimposed throughout the duration of the trial. By the end of the trial, there were 805 subjects with at least 1 positively adjudicated MACE class event, 406 in the lixisenatide group and 399 in the placebo group.

The incidence rates were 6.39 and 6.31 per 100 patient-years for lixisenatide and placebo group respectively. Using the prespecified Cox proportional hazard model, the hazard ratio estimate was 1.02 with an associated 95 percent confidence interval of 0.89 to 1.17. The upper bound of the 95 percent confidence interval was significantly lower than 1.3 at the two-sided alpha of 0.05 significance level.

The lower portion of the table shows that the first MACE-plus events were mostly non-fatal myocardial infarctions with only around 0.3 percent of first events being hospitalizations for unstable angina events.

The table here summarizes analyses on the

ITT population for both MACE-plus and MACE using the two censoring schemes, the primary censoring scheme on study on the top, and sensitivity censoring scheme on treatment as the bottom. Overall, the finding that ELIXA ruled out the 1.3 risk margin was consistent across endpoints and censoring schemes.

This figure presents Kaplan-Meier curves of time from randomization to death from any cause for lixisenatide and placebo. Overall, the two curves were superimposed for the duration of the trial. A total of 434 deaths were observed with 211 in the lixisenatide group and 223 in the placebo group.

The prespecified COX proportional hazard model for time to on-study all-cause mortality resulted in a hazard ratio estimate of 0.94 for lixisenatide versus placebo with two-sided 95 percent confidence interval of 0.78 to 1.13. When only the death in the on-treatment period was investigated, the results were similar.

In summary, the ELIXA trial was a randomized, double-blind, placebo controlled,

event-driven cardiovascular outcome trial designed to rule out a cardiovascular hazard ratio of 1.3 or above for lixisenatide compared to placebo. My review did not find any major statistical issues on the design, conduct and analysis of the primary and the secondary endpoints.

The estimated hazard ratio for the primary MACE-plus endpoint was 1.02 with 95 percent confidence interval of 0.89 to 1.17. The upper bound of the 95 percent confidence interval was significantly lower than 1.3. Therefore, the ELIXA trial demonstrated that lixisenatide was not associated with a 30 percent or greater relative increase in cardiovascular risk as specified by the 2008 FDA guidance.

This ends my presentation. Thank you for your attention. I will hand over to Dr. Balakrishnan now.

FDA Presentation - Suchitra Balakrishnan

DR. BALAKRISHNAN: Having discussed the lixisenatide product, I will now turn to the presentation of the insulin glargine and

lixisenatide fixed-ratio combination. In the FDA background document, it was referred to as the fixed-ratio combination or FRC. For this presentation, I will be referring to it as iGlarLixi.

iGlarLixi is a combination of insulin glargine and lixisenatide. The two drug substances are combined into a single dosage form. The applicant is proposing to use two different ratios in two different pen injectors. Each pen injector will contain 3 mL of the combination.

The first, which I will refer to as pen A, will have a ratio of 2 units of insulin glargine for every 1 microgram of lixisenatide. The second, which I will refer to as pen B, will have a ratio of 3 units of insulin glargine for every 1 microgram of lixisenatide.

The pen injectors will display the dose in terms of units of iGlarLixi. This number corresponds to the number of units of insulin glargine delivered. Each of the pen injectors has a recommended dose range, 10 to 40 units of

iGlarLixi for pen A and 30 to 60 units of iGlarLixi for pen B.

The recommended dose range allows for administration of lixisenatide doses ranging from 5 to 20 micrograms. The dose is displayed in terms of units of iGlarLixi and the black region with white lettering is outside of the recommended range.

In this representation of the dial, the display of the doses would proceed in the order shown by the red line. The lowest selectable dose for each pen injector allows for a selection of 1 unit of insulin and a corresponding lixisenatide dose of 0.5 or 0.3 micrograms, depending on the pen that is used.

The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

In patients not previously treated with insulin, the proposed starting dose will contain 10

units of insulin glargine and 5 micrograms of lixisenatide. Note that for those patients already on GLP-1 receptor agonist therapy, this would lead to a reduction in the dose of the GLP-1 component.

For patients already on basal insulin, the applicant proposes a starting dose based on the previous basal insulin dose. If the basal insulin dose is below 24 units, the patients should start on a dose of 10 units of insulin glargine and 5 micrograms of lixisenatide.

If the basal insulin dose is between 25 and 40 units, the patients should start at 20 units of insulin glargine and 10 micrograms of lixisenatide. If the basal insulin dose is between 40 and 60 units, patients should start at 30 units of insulin glargine and 10 micrograms of lixisenatide. This approach results in a reduction in the dose of insulin.

The design of the pen injectors results in an overlap in the recommended dose range when patients are prescribed 30 to 40 units of insulin glargine.

In this range, switching between pens results in differences in the lixisenatide dose. While in the clinical studies patients used pen A in this range but were advised to switch to pen B, if there were issues with gastrointestinal tolerability. The proposed prescribing information does not provide specific information on this overlap range but recommends switching from pen A to pen B for doses over 40 units.

There were two phase 3 studies conducted to support the efficacy of iGlarLixi. Study EFC12404 was a 30-week open-label active control study in patients not previously treated with insulin. Study subjects were randomized to iGlarLixi, insulin glargine or lixisenatide. Patients were allowed to continue metformin but other oral anti-diabetic drugs were discontinued.

Patients in the iGlarLixi and insulin glargine groups started at a dose of 10 units of insulin glargine. The dose was then titrated based on fasting glucose targets. Patients in the lixisenatide group started at a dose of 10

micrograms for 2 weeks and this was then increased to 20 micrograms for the remainder of the study.

Study EFC12405 was a 30-week open-label study in patients uncontrolled on basal insulin. All patients were switched to insulin glargine following a 6-week titration stabilization period. Patients were randomized to iGlarLixi or to continue insulin glargine. Non-metformin oral anti-diabetic drugs were discontinued.

Patients in the iGlarLixi group had the insulin glargine component reduced to half to two-thirds of the baseline dose. They also had to be on a 10 microgram dose of the lixisenatide component.

Since it was difficult to satisfy both criteria, initiation dose deviations were reported for 27 percent of patients. The dose was to be unchanged for 2 weeks and then could be titrated to fasting glucose targets.

Patients in the insulin glargine group continued the insulin glargine dose at baseline and were to titrate their insulin dose to achieve

fasting glucose targets. Both studies used the same titration algorithm. The titration algorithm limited increases to an insulin dose to no more than 40 units per week.

Dr. Jiewi He will now present the statistical findings for efficacy.

FDA Presentation - Jiwei He

DR. HE: Good morning. My name is Jiwei He. I'm a statistician from the Office of Statistics. I will be presenting the statistical assessment of efficacy for the iGlarLixi application.

The primary efficacy endpoint in both phase 3 studies was change in HbA1c from baseline to week 30. The prespecified primary analysis was a mixed-effects model with repeated measures including all available observations regardless of treatment discontinuation or initiation of rescue therapy. Key secondary endpoints include a change in 2-hour glucose excursion and a change in body weight.

These tables show patient dispositions in the two studies. In study 404, the lixisenatide

group showed more discontinued treatment due to adverse events compared to the other two treatment groups, 12.0 percent versus 6.2 percent and 5.8 percent.

In study 405, the iGlarLixi group showed more discontinued treatment due to adverse events compared to the insulin glargine alone group, 7.9 percent versus 2.7 percent. The low percentage of treatment discontinuation in the insulin glargine alone group was probably due to the fact that the patients in this study were already on basal insulin at the time of enrollment.

In the protocol, the investigators were encouraged to continue collecting measurements after treatment discontinuation. The actual percent of patients missing their HbA1c measurement at week 30 was around 5 percent in each treatment group, as can be seen from the red numbers.

I verified the applicant's primary analysis results. iGlarLixi demonstrated a superiority to insulin glargine and lixisenatide in terms of change in HbA1c from baseline to week 30.

The mean difference of iGlarLixi versus insulin glargine was minus 0.29 percent in study 404 and minus 0.52 percent in study 405. So the difference of iGlarLixi versus insulin glargine appeared to be larger in study 405 where the patients were uncontrolled on basal insulin.

In each study, the percent of patients with missing data for the primary endpoint was quite low, around 5 percent, and was similar between treatment groups. For study 404, the applicant conducted a sensitivity analysis imputing missing values from patients who discontinued treatment based on the retrieved dropouts. The results from the sensitivity analysis were very close to those from the primary analysis.

For study 405, the applicant stated that a number of the retrieved dropouts were not sufficient to build a reliable imputation model. In order to tip statistical significance of the results, unrealistic assumptions about the missing data need to be made. In summary, missing data did not appear to have much impact in this application.

There were some major concerns. First, lixisenatide and iGlarLixi ranges from 5 to 20 micrograms. The contribution of low-dose lixisenatide to the effect of iGlarLixi is uncertain. In order to address this problem, the applicant conducted a subgroup analysis of HbA1c change by final insulin dose category, which I will comment on in later slides.

Second, the external validity of the results to the practice of the treatment of type 2 diabetes is uncertain. Insulin glargine dose was capped at 60 units in the insulin glargine alone arm. This cap, together with the limitations of the insulin titration algorithm, raised the concern that the treatment difference observed in the phase 3 studies may not reflect actual treatment difference in practice.

The applicant conducted a sensitivity analysis with respect to insulin dosing. Dr. Balakrishnan will elaborate on this point at the end of her presentation.

The applicant examined HbA1c change in each

subgroup defined by final insulin dose category. Final insulin dose is a post-randomization variable and it is affected by assignment of treatment. Differences between iGlarLixi and the insulin-glargine alone groups within each final insulin dose category no longer represent treatment effect. Therefore, the differences cannot be used to make inference about a contribution of lixisenatide in iGlarLixi.

Also, there was not enough data about patients receiving low-dose lixisenatide. This table shows the number of patients by final lixisenatide dose category in each study. Due to the design of the study, there were few patients receiving lixisenatide at doses below 10 micrograms in study 405. Fifty-eight patients received lixisenatide at doses below 10 microgram in study 404.

This graph shows the mean change in HbA1c by final insulin dose category in study 404, which I adapted from the applicant's results. It is technically not right to compare between treatment

groups by final insulin dose category.

Even if we disregard this problem and assume the treatment groups were comparable within each final insulin dose category, the difference between treatment groups in the lower-dose categories did not appear to be very big, particularly with the lowest-dose category, which corresponds to lixisenatide, 5 to 10 microgram in the combination product. Therefore, the contribution of low doses of lixisenatide to the effect of the combination product on HbA1c change is not clear.

In order to address the external validity problem, the applicant conducted a tipping-point analysis to evaluate the potential impact on HbA1c results had insulin doses greater than 60 units being allowed in the insulin-glargine-alone arm. Various additional HbA1c reductions were added to all the observe the post-baseline values for the insulin-glargine-alone patients having a final insulin dose of 60 units.

The same MMRM model was used as in the primary analysis. For those patients in the

insulin-glargine-alone arm having a final insulin dose of 60 units, additional reduction in HbA1c of 0.9 percent for study 404 and 1.3 percent for study 405 would have been needed for the results to be no longer statistically significant. Dr. Balakrishnan will discuss these results further.

In conclusion, iGlarLixi demonstrated a superiority to both insulin glargine and lixisenatide in terms of change in HbA1c from baseline to week 30 in the applicant's phase 3 studies. Overall, both components appeared to contribute to the effect of the combination product.

The contribution of low doses of lixisenatide to the effect of iGlarLixi on HbA1c change is uncertain. And there are concerns about the external validity of the results to real practice. Thank you.

FDA Presentation - Suchitra Balakrishnan

DR. BALAKRISHNAN: Dr. He has discussed efficacy issues related to the primary endpoint. I will now discuss efficacy findings for some of the

secondary endpoints, the safety findings, the generalizability of these findings to clinical practice, and, finally, the practicality of combining a GLP-1 receptor agonist and a basal insulin.

Change in body weight was assessed in both studies as a secondary endpoint. In study EFC12404, lixisenatide-treated subjects had a mean reduction in body weight of 2.3 kilograms. The insulin glargine group had an increase of 1.1 kilogram and the iGlarLixi group was essentially unchanged. In study EFC12405, the weight was relatively unchanged in both groups. There was an increase of 0.7 kilograms in the insulin glargine group, and a decrease of 0.7 kilograms in the iGlarLixi group.

While we recognize that weight effects are an important consideration for patients and prescribers when selecting therapies, we do not know if the weight findings from these studies are clinically meaningful. One reason is that the overall change in weight was small. The treatment

difference between iGlarLixi and insulin glargine was less than 2 kg, or 1.5 percent.

Now, whether small difference has a meaningful impact on patients in terms of improving clinical outcomes or in terms of quality of life is unclear. These studies were not designed to address these questions. Additionally, the weight observation is for a relatively short period of time.

For context, studies to assess drugs intended for weight management typically look at the effect after 52 weeks. Whether these small changes would persist over time and what significance this has over the life of a patient with diabetes is unclear.

Post-prandial glucose was assessed using a standardized liquid meal test. This was performed in the morning at baseline and at week 30 after administration of study drug. Both lixisenatide and iGlarLixi resulted in a decrease in the degree of glucose expression at week 30 compared to baseline. The mean change from baseline was

largest for lixisenatide followed by iGlarLixi. The insulin glargine group was essentially unchanged.

While there appears to be a contribution of lixisenatide on post-prandial glucose, it is unclear how much that contributes to the change in HbA1c. Further, it is unclear whether this post-prandial effect persists beyond the first meal.

In this figure from a pharmacodynamic study in the lixisenatide program, 24-hour plasma glucose profiles are shown. The solid red line shows the baseline profile for the lixisenatide-treated patients. The drug was dosed in the morning before the standardized meal. The dashed red line shows the profile after 28 days of lixisenatide.

From this study, it appears that there is an effect of lixisenatide on post-prandial glucose after breakfast, but later in the day, there is no apparent effect. The green line is the comparator data. Additionally, the effect of targeting post-prandial glucose on clinical outcomes has not

been established in randomized clinical trials.

Having discussed some of the secondary efficacy endpoints for iGlarLixi, I will now briefly discuss the safety findings. The development program for iGlarLixi was limited and included two phase 3 studies with around 462 patient years of exposure to iGlarLixi. The safety database is further limited by the short duration of the studies.

My discussion of safety will be limited to common adverse events. The database was not adequate to consider other rare events such as serious hypersensitivity reactions or pancreatitis. Inferences about safety concerns related to these issues has to be based on the lixisenatide clinical program. Some concurrent use data for concurrent use of insulin glargine and lixisenatide 20 microgram is available from the lixisenatide program.

Safety concerns for insulin glargine include hypoglycemia and weight gain. Safety concerns for the GLP-1 class include gastrointestinal adverse

events, pancreatitis, and increases in heart rate. Both insulin glargine and lixisenatide carry concerns for immunogenicity and injection-site reactions. iGlarLixi would be expected to carry both sets of risks.

The most common adverse events were consistent with that seen in the lixisenatide program. Nausea and vomiting was most common in the lixisenatide group, followed by the iGlarLixi group. Other common adverse events included diarrhea and headache. Both of these also occurred more commonly with lixisenatide followed by iGlarLixi, with the lowest incidence occurring in the insulin glargine group.

American Diabetes Association definitions were followed for hypoglycemia. The lowest incidence of hypoglycemia was in the lixisenatide group. The incidents were similar with insulin glargine and iGlarLixi. Of interest, severe hypoglycemia was more frequent with iGlarLixi compared to insulin glargine in study EFC12405. There were 5 events in 4 patients with iGlarLixi

compared to only 1 event with insulin glargine.

Having covered the efficacy and safety findings, I will now discuss the generalizability of these findings to clinical practice. The trials were designed to address a regulatory question, which is what is the contribution of each individual component to the total effect.

While the studies suggest that, overall, there is a contribution of each component, there are concerns about the contribution of lixisenatide across the dose range. There are also concerns regarding generalizing the findings to clinical practice. These stem from the titration algorithm, the success of titration in the studies, and the cap on the insulin dose.

As discussed by Dr. He, there is uncertainty in terms of the contribution of lixisenatide in the low-dose range to glycemic control. In considering that there may not be benefit from the lixisenatide component in the low-dose range for iGlarLixi, it is also important to consider safety in that range. Adverse events reported in the first 42 days of

study EFC12404 were considered to explore the safety in the low-dose range.

As all subjects in this study started at a dose of iGlarLixi that contained 5 micrograms of lixisenatide, the early period should correlate to the safety of the low-dose range. In looking at this subset, adverse events were again consistent with the GLP-1 class.

The lixisenatide arm had the highest incidence, with iGlarLixi again having the second highest incidence. The incidence with iGlarLixi remained higher than insulin glargine. This raises the question of whether there is a positive benefit risk at this range.

We have reservations about the efficacy conclusions of superiority to a titratable product. One reason is whether the titration was robust enough to achieve titration targets and the potential for bias. The titration algorithm used in the phase 3 studies was relatively conservative. Titration occurred once a week based on the median fasting glucose in the preceding 3 days. Increases

in dose were limited to no more than 4 units per week.

Whether a different titration algorithm that allowed for more rapid titration, like the one used previously by the applicant in the early treatment diabetic retinopathy study, would have resulted in better glycemic control is unknown.

An additional concern is whether it's fair to use the same algorithm to titrate the dose of one drug versus titrating the dose of two drugs.

The success rate of titration in the study also raises the question about the generalizability of the study results to clinical practice. Despite having an algorithm and central monitoring, successful achievement of titration targets was less than 40 percent in study EFC12404. In study EFC12405, the fasting glucose targets were achieved by approximately 30 percent of patients.

The results for not obtaining goal are unclear. As a result, there is uncertainty with regard to whether the achieved HbA1c accurately reflects the ability of treatment to improve

glycemic control.

Whether a more robust titration algorithm would have resulted in a higher proportion of subjects achieving fasting plasma glucose targets is unknown. Whether superiority of iGlarLixi compared to insulin glargine alone will continue to be seen is also unknown.

An additional concern is the cap in the insulin glargine dose. In practice, insulin can be titrated without a limit. In the phase 3 studies, the dose was capped at 60 units for both iGlarLixi and for insulin glargine. While this reflects the limit of the proposed drug product, it raises questions with regard to the clinical relevance of the study findings.

In the phase 3 studies, approximately 16 to 30 percent of subjects were at the 60 unit limit. The mean fasting glucose in this subgroup was not at the titration target of 80 to 100 milligrams per deciliter. As Dr. He has discussed, the applicant's tipping point analysis for this subgroup suggests that the insulin glargine

subjects would have needed a further reduction in Hb1Ac of close to 1 percent to not be able to conclude superiority.

Whether further titration beyond 60 units of insulin glargine would have resulted in this amount of further reduction in HbA1c is unknown. How much this means with regard to the contribution of capping the dose on the superiority conclusion is also unclear.

As has been discussed, the titration of dose may bias the superiority conclusion. If we consider the entire study population, the insulin glargine arm would have needed an additional HbA1c reduction of 0.2 percent in study EFC12404 and 0.4 percent in EFC12405 to no longer conclude superiority.

The agency has some additional concerns with regard to the iGlarLixi product that relate to the practicality of this approach to combining a GLP-1 receptor agonist with a basal insulin. iGlarLixi combines two active ingredients with different terms of measure, the units for insulin glargine

and micrograms for lixisenatide.

Designating the dosing in terms of units only references the insulin component, insulin glargine, and does not communicate the presence of the GLP-1 component. This could lead to confusion and medication errors in the clinical setting such as overdosing on the GLP-1 component by adding a second GLP-1 agonist or by using iGlarLixi like a titratable product with no upper dose limit.

The proposal to use 2 pen injectors also raises the potential for confusion. Whether patients and prescribers will recognize the differences between the 2 pen injectors and when to use each one is unclear. iGlarLixi also results in loss of dose flexibility. It is not possible to adjust the dose of one without adjusting the dose of the other one.

Further, the insulin dose is capped. This is in contrast to using a once-weekly GLP-1 receptor agonist with basal insulin, which would offer the convenience of fewer injections while still allowing for unrestricted titration of the

insulin.

The rationale for decreasing the dose is unclear. In patients already on a GLP-1 agonist or on basal insulin, this leads to a decrease in the dose of the previous component. Additionally, when transitioning from pen A to pen B, there is a decrease in the lixisenatide component. While the applicant has performed two studies to demonstrate the efficacy of iGlarLixi, it is worth noting that some potentially informative scenarios were not studied. These were not required, but would have answered clinically interesting questions.

iGlarLixi has not been compared to lixisenatide at the maximally effective dose plus insulin glargine titrated to maximal effect. An understanding of this comparison may be informative for patients and prescribers as they consider combining a GLP-1 receptor agonist and a basal insulin.

iGlarLixi has not been studied in patients requiring additional glycemic control despite GLP-1 receptor agonist therapy, nor has it been studied

in patients already treated with basal insulin and a GLP-1 receptor agonist. These are both potential scenarios when use of iGlarLixi may be considered.

An additional consideration is where does this product fit in the approach to treatment. In considering how to treat patients with diabetes, two general approaches can be considered. In the first, drug therapies are added one at a time, depending on the level of glycemic control.

In the other, multiple drugs can be added at once. Clinical guidelines do not necessarily agree on how to approach drug therapy. Some clinical guidelines have recommendations on when starting multiple therapies at once should be considered, while others do not recommend this approach. Even those guidelines that have recommendations about starting multiple agents at once do not necessarily agree on when to do this.

Next, Dr. Ariane Conrad will discuss the human factors testing which was performed.

FDA Presentation - Ariane Conrad

DR. CONRAD: Good morning. My name is Dr.

Ariane Conrad and I'm a safety evaluator with the Division of Medication Error Prevention and Analysis. I will present DMEPA's evaluation of the human factors validation study for insulin glargine, lixisenatide, which I will refer to as iGlarLixi for the purposes of this presentation.

My presentation will describe iGlarLixi's product characteristics, provide a brief review of human factors testing and its purpose, and provide a summary of the results from the human factors testing conducted for iGlarLixi.

iGlarLixi is a fixed-ratio, multi-ingredient product that contains a long-acting insulin product and a GLP-1 agonist in a single pen device. It is to be available in 2 pen devices containing two different ratio actions of insulin glargine to lixisenatide, 2:1 ratio for the pen designated as pen A and 3:1 ratio for the pen currently designated as pen B.

This is an illustration of the recommended dose range for each of the two proposed pen injectors. You can see that there is an overlap in

the doses that can be dialed for each pen.

Also, it is important to note the difference in the lixisenatide dose for the insulin units dialed on each pen. For example, you can see that a dialed dose of 30 units contains 15 micrograms of lixisenatide if pen A is used, while the same 30-unit dose on pen B will contain 10 micrograms of lixisenatide.

In this example, you would expect a difference in glycemic control because of the differences in the dose of lixisenatide. This product design is atypical since we would expect that the lower concentration product would be recommended for use prior to titrating up to the higher concentration product. However, this is not the case with this product.

The proposed dosing strategy for iGlarLixi is based on the patient's previous use of oral anti-diabetic agents, or previous insulin requirement. These tables are in the dosage and administration section of the proposed prescribing information for iGlarLixi and illustrate the

initiation dose strategy recommended if converting patients from oral agents or basal insulin to iGlarLixi.

Of note here is that the recommended starting dose and the recommended pen device for this product is based on the patient's previous medication use.

Based on the information in the first dosing table, patients that are converting from any anti-diabetic agent, besides basal insulin, will be started on 10 units of pen A once daily. If patients are converting from basal insulin, the starting dose in the pen device will depend on their previous dose of insulin.

Of note, if a patient was on a basal insulin dose that was greater than 40 units prior to switching to iGlarLixi, the recommendation per the prescribing information is to lower the starting dose to 30 units using pen B.

Pictured here are sample pen injectors provided by the applicant to aid in our review of the product. The pens use the SoloSTAR device

platform currently used for other marketed products. The images on the top right and bottom depict what the pens will look like in a closed position and then the dialed-out position for dosing.

As discussed previously by Dr. Balakrishnan, using the image on the left, there are numbers on the pen dial that are on a blackened background and this is meant to indicate the doses that are not recommended for use on this pen. However, these doses can be dialed on the pen.

In addition to the proprietary name, the applicant intends to use color to help differentiate between the 2 pen devices.

In the process of reviewing this product, we identified a number of aspects to consider for iGlarLixi. First, the two active ingredients in this product are dosed using different terms of measure, units for the insulin component and micrograms for lixisenatide. However, the pen device dials dosage based on units of insulin alone without indicating the respective lixisenatide

dose.

The applicant proposes to label the product's dose in units and to simplify the expression of dose on this product in labeling by focusing the dose on the insulin component alone. Designating a dose in terms of units and labeling could potentially mislead practitioners since it only references the insulin component and does not impart the presence of the GLP-1 component.

The use of both dosage terms would probably be confusing for users, so the best strategy is unclear. However, if dosing in the prescribing information and on the pen device were to express both active ingredients, it would be cumbersome. Of note, the applicant has conducted human factor studies using the term "units" and users demonstrated understanding based on the results that we will discuss later.

Second, there is a risk for drug duplication if users are not aware that this product contains two components, especially considering that the dosing is based solely on the insulin component.

Also, we noted that the 2 pen devices are designed to deliver two different fixed ratios of insulin and lixisenatide and cannot be substituted for one another. So if the wrong pen is prescribed or dispensed, patients would receive the wrong dose of lixisenatide, which could result in either a lower or higher than intended dose of lixisenatide.

The fourth consideration is that 1 pen delivers from 1 unit to 40 units, and the other pen delivers doses up to 60 units, again based solely on the dose of the insulin glargine. Based on the proposed dosing in the prescribing information, there is an overlap in the dosing between the pens for all doses from 1 to 40 units.

The prescribing information does recommend using pen B for doses that are greater than 30 units, but the overlap for doses between 30 and 40 units can create ambiguity as to which pen should be used for patients requiring doses within this range.

The last consideration that we identified was that there is a dosing limit of 60 units of

insulin glargine for this product due to the maximum recommended dose of 20 micrograms of lixisenatide.

Considering that type-2 diabetic patients are insulin resistant, they may require insulin glargine doses greater than 60 units. And prescribers may attempt to prescribe doses that are larger than 60 units since this can be appropriate for long-acting insulin products, which do not have maximum doses.

Now I'd like to talk about human factors testing. The purpose of human factors testing is to demonstrate that the product can be used by the intended user groups without serious use errors when used as intended and under expected use conditions. These studies are typically designed to evaluate how users interact with the product, including the different components of the product labeling, such as the instructions for use, package insert, and carton labeling.

The human factors testing is designed to test participants that are representative of the

actual users of the device. We would expect for these studies to include a minimum of 15 participants to represent each distinct user group. In addition, testing should include all critical tasks necessary for safe use of the device, the final product design and test conditions that simulate actual conditions of use.

Human factors testing provides data that we review to understand what representative users do when they use the product and determine if changes to the product design and/or product labeling are necessary for risk reduction.

Given that the sample sizes used for human factor studies are very small, even one error could identify an unexpected use behavior that was not previously identified during the product design process. In this case, assuming that no changes were made to mitigate the error, we would expect that other users of the product will make the same error.

To clarify further, a single error in human factors studies can indicate a problem with the

product's design or labeling that we would expect would be problematic with actual use by larger numbers of users.

Next, I will review the human factors study that was conducted for iGlarLixi. The applicant conducted two studies to evaluate device usability and prescriber comprehension for iGlarLixi. First I will discuss the prescriber comprehension study.

The study was designed to evaluate prescriber comprehension of the prescribing information and user understanding of the numerical modifiers proposed for use within the proprietary name. It was conducted with 15 prescribers to evaluate prescriber comprehension.

The key task for this aspect of the study was designed to provide data to support that prescribers can prescribe and interpret the meaning of the proprietary named modifiers. In the prescribing task, physicians were asked to provide prescriptions for each of the four individualized patient case scenarios based on the prescribing information.

The device usability study was designed to evaluate the ability of the intended users to properly use the iGlarLixi pen. It was conducted with 15 pharmacists, 15 nurses who treat and train diabetic patients, and 30 patients with diabetes to determine their ability to properly use the pen injectors.

The key tasks as addressed by the study were designed to simulate use tasks and provide data to support that users can dispense, differentiate,, and correctly interpret the meaning of the proprietary name modifiers. The study focused on the specific tasks that were different from those that are for the currently marketed SoloSTAR pen injectors that are approved for use in other medications instead of testing every aspect of use of these pen devices.

We agreed with this approach, as the applicant was relying on human factors validation data and post-marketing information gathered from the currently marketed SoloSTAR pens.

For the dispensing task, pharmacists were

presented with a prescription for either of the two proposed pen options. Then they were asked to demonstrate the ability to dispense the correct iGlarLixi pen.

For the differentiation and handling tasks, patients and nurses were asked to identify the correct iGlarLixi pen, select the correct pen when presented with different dose regimens, and prepare an assigned dose using the correct pen. Of note, none of the study participants received training on the medication or pen injector prior to completing the study tasks.

This table summarizes the results for each of the tasks tested in the study. As a reminder, when you're reviewing human factor study results, every error is evaluated to determine the cause of the error and the associated clinical consequences to help us determine if modifications are necessary.

Of note, there was one error in the dispensing task and one error in the pen handling task. I will discuss these errors in further

detail in the next few slides.

The results of the prescribing task indicated that all 15 physician participants understood the prescribing information and were able to prescribe the correct dose of iGlarLixi in the correct device for the individualized patient case scenarios tested.

In the study, physicians were given unlimited time to review the prescribing information prior to answering the case questions, and they were specifically directed to answer the case questions based on the directives provided in the prescribing information.

We recognize that it would be difficult to simulate within the context of a human factors validation study what prescribers would do prior to prescribing any product and the amount of time some prescribers would take to review the prescribing information.

Also, prescribers in the study were tested on their ability to answer the questions based on the prescribing information instead of using the

information as they would if they were actually planning to prescribe a product to a patient in clinical practice.

Although we acknowledge that the testing conditions may not completely simulate actual prescribing of the product, we would expect prescribers to familiarize themselves with important information about the product prior to prescribing it for the first time.

Additionally, since the study was designed to assess understanding of the label contents, reviewing the prescribing information prior to prescribing was necessary and reasonable to determine if prescribers are able to prescribe the correct dose and device.

The results of the dispensing task indicated that 14 of the 15 pharmacist participants selected the correct package. One pharmacist participant initially selected the wrong product when presented with the prescription for one of the iGlarLixi pen options because the pharmacist misunderstood the task. When the task was clarified, this

participant selected the wrong iGlarLixi pen.

The applicant attributed this error to the pharmacist participant overlooking the numerical modifier in the proprietary name that is meant to differentiate between the 2 pens. This data indicates that the availability of 2 pens could lead to the potential for selecting the wrong product within the product line that could result in a patient receiving the wrong dose.

The results of the differentiation tasks indicated that all nurse and patient participants identified the correct pen. For the handling tasks, 44 of the 45 participants selected the correct pen to use and prepared the correct dose when presented with different dose regimens. One patient participant failed this task by preparing 10 units for the dose instead of the 20 units instructed to prepare. This patient reported confusing the numerical modifier within the proprietary name with the assigned dose.

The applicant had initially proposed two different numerical modifiers, 1 for pen A and one

for pen B. Our analysis determined that this error occurred due to confusion with the proposed numerical modifiers within the proprietary name. These modifiers were found unacceptable by the agency and this issue remains unresolved at this time. We are currently working with the applicant to determine appropriate proprietary name alternatives.

In summary, we have some residual concerns with regard to the potential for errors, particularly given the proposal to market two different pen injectors with two different ratios for the components.

While the proprietary name for the 2 pens has not been established and the product proprietary name modifiers may be useful to distinguish between the 2 pens, the availability of 2 pens may still be associated with risk that may not be completely mitigated through proprietary names and product labeling. Marketing only one pen injector would minimize the risk of error and eliminate the need to distinguish between the two

products.

In addition, we acknowledge that simulated-use human factor studies may not fully represent actual use conditions. Therefore we have residual concerns that the simulated-use conditions employed in human factors testing for iGlarLixi may not reflect prescribers' actual use of the prescribing information to initiate therapy.

This concludes my presentation. Thank you for your attention.

FDA Presentation - Suchitra Balakrishnan

DR. BALAKRISHNAN: I will now summarize FDA's conclusions for lixisenatide and iGlarLixi. Lixisenatide was studied as a once-daily injection of 20 micrograms. Lixisenatide was statistically superior to placebo in reducing HbA1c. The safety profile was generally similar to other GLP-1 receptor agonists. Gastrointestinal symptoms were the most common adverse reaction. Cardiovascular risk was neutral.

Lixisenatide may be more immunogenic. There is a high incidence of anti-drug antibodies.

Neutralizing and cross-reactive antibodies may impact efficacy and safety. There is a possible clinical risk of hypersensitivity reactions, such as anaphylaxis.

iGlarLixi was statistically superior to lixisenatide alone or insulin glargine alone in the two phase 3 studies. The studies address a regulatory question. There is concern for impact of capped insulin dose and adequately of titration on clinical generalizability. There is uncertainty regarding additional benefit of lixisenatide at low doses.

Clinical considerations include the potential for medications errors. This is a multi-ingredient product combining ingredients with different units of measurements. There are 2 pen injectors. There is a loss of flexibility, where change in the dose of one component is not possible without changing the other.

There is restriction on the insulin dose. Some scenarios were not studied, such as iGlarLixi compared to GLP-1 agonist at established effective

dose and titratable insulin. The place where the product fits in the approach to the treatment of type 2 diabetes is unclear.

Thank you for your attention.

Clarifying Questions to FDA

DR. SMITH: I'd like to thank the FDA for these presentations. And we now have some time for clarifying questions. I know there was some carry-over from this morning, but I'd like to first focus on clarifying questions for FDA. Dr. Yanovski?

DR. YANOVSKI: Yes, thank you. And this goes back to something Dr. Seely asked before. I'm trying to understand the efficacy of lixisenatide, first of all, just even as monotherapy. And in Dr. Balakrishnan's presentation on the slide on page 8 of efficacy and active control studies of lixisenatide, am I correct that, in a head-to-head comparison with exenatide, lixisenatide was inferior?

DR. CHONG: The primary objective was to demonstrate non-inferiority and they met that

objective. Looking at the statistical findings, it does suggest that it is inferior to exenatide BID.

DR. YANOVSKI: And also, you could not rule out non-inferiority, is that correct, between lixisenatide and insulin glulisine?

DR. CHONG: So for that study, non-inferiority was demonstrated against glulisine once a day. Compared to 3 times a day glulisine, the primary analysis suggested it was non-inferior, but the sensitivity analyses raised a question about the robustness of that finding.

DR. YANOVSKI: Particularly, I think, in the study that the sponsor presented, study 404, in their slide 44, it looked like only 33 percent of patients who were on lixisenatide met their hemoglobin A1c goals. So I just had concerns, listening to the presentation, about the efficacy of lixisenatide compared with other GLP agonists and other anti-diabetic medications.

DR. SMITH: Dr. Nason?

DR. NASON: I had a couple questions. The first one I'd like to ask is about the slide 28

that was looking at the injection-site reactions in lixisenatide. And I was wondering, is this -- I didn't quite understand this table. Maybe I'll pause for a second. Sorry. It's from the safety of just the lixisenatide by itself, slide 28.

DR. SMITH: Can we get that slide up?

DR. NASON: My question basically, while it's loading, was whether this was a time-dependent model, or this was the slide that looked at injection-site reactions by antibody status and whether this was only looking at site reactions that happened after the antibody, or whether people were classified as ever having an antibody, or how those categories, both for reaction and for antibody, were chosen. Are people in that table multiple times for different injections?

DR. BALAKRISHNAN: Actually, this was antibodies. Well, this reflects the patients. The first table shows those who had antibody status, positive or negative. The second, the bullets, sub-bullets shows those who had positive antibody concentrations. Now, these were measured at

prespecified time points. I think the sponsor can elaborate on when they were measured.

DR. SMITH: Dr. Meisel?

DR. MEISEL: I have three questions. I think they'll all be very fast. Is the FDA aware of any other combination or ever approved a combination drug where the individual ingredients were not independently studied together?

DR. GUETTIER: Could you just clarify your question? I'm not sure I understand.

DR. MEISEL: In this case we don't have any data that -- we don't have a study that looked at lixisenatide plus glargine independently put together versus whatever. But instead, we have a combination product studied by itself, but not as lixi plus glargine independently put together.

DR. GUETTIER: Right. I think that, in general, the fixed-dose combination that we review combined dosages that are already approved. So most of the time, we compare two products at doses that are going to be used and approved versus single-entity products.

For this particular product, the applicant basically has to meet the combination rule, which is to show that both components within the combination product contributes to the claimed effect.

As was stated by the applicant, this was a little tricky in this application because, again, most combination drugs combine the same types of active ingredients. So they'll combine a fixed dose with a fixed dose. So two fixed doses are easily studied as a factorial study.

This combines a fixed dose with a titratable product. And so when selecting how to show contribution to claimed effect, we had to decide whether or not we were going to follow a paradigm of a titration product, so comparing titration to titration versus a completely artificial setting of basically setting the dose of lixisenatide to 0.4 milligram and Lantus to 10 without changing it for the length and duration of the study, that would not have been reflective of practice.

When we had discussions with the applicant,

we felt that it was reasonable to follow titration approach.

So what the applicant really has to do is show contribution to claimed effect. If they're able to do that, which is usually a superiority on the primary outcome of the study, they meet the regulation.

DR. MEISEL: I guess it's a little bit more difficult question than I anticipated. The second question is, is there any other drug, combination drug on the market with two active ingredients where the dose is referred to only with one of them as opposed to with both of them?

DR. MERCHANT: I can address that. So we looked at the products that are available in the market where there are two active ingredients. The doses are expressed in different terms of measure, such as this one, units and micrograms. And what we found is that the dosing of that product is expressed in a standard unit, either the dosage form, like one tablet, or one application as such.

So in this case, it's atypical. It's

different from the other products that are out there because the dosing has to be expressed in both units, and I guess terms of measure for one is units and one is micrograms, so it makes it more complex.

DR. MEISEL: So nothing else exists out there. This would be a first. Nothing else exists out there that would have two active ingredients of units of measure that we're only talking about it in terms of Lantus units equivalence in this case? Nothing else like that exists?

DR. MERCHANT: So let me clarify your question. Are you asking whether there are products out there with different terms of measure or just different multi-ingredient products out there?

DR. MEISEL: I know there's lots of multi-ingredient products out there like vitamins that have a million ingredients, and we just call it one multivitamin. I call it one tablet. But in this case, we're talking about individualizing doses and everything else that I know of has 75/50

or 500/250, whatever it may be. This is the only one that we're proposing to ignore the contribution of the milligrams or the units of one in favor of only referring to the second one.

DR. MERCHANT: That's what the applicant is proposing at this time. So they're referring -- and we recognize that referring to both terms of measure might be complex, and you know when you --

DR. GUETTIER: I mean, I think you're correct. I think that there are products out there that combine things that have different units, but usually it's a simple way to describe it. As a tablet, take one tablet a day. Or apply the product on the skin, for example. That's possible to do for these products. We're not sure yet that it's possible to do for this product.

DR. MEISEL: Okay. And the third, harder than I thought question is, are there any other products on the market that are intended to dial or deliver a dose where you can deliver a dose less than what is recommended to be the minimum dose?

DR. MERCHANT: No, we are not aware of any

other products. Typically, insulin pens are the one where you dial the dose and they are recommended for the entire range of dosing. So whatever they can dial, they are recommended, the dosing.

DR. MEISEL: So this would also be a first?

DR. MERCHANT: This will also be the first.

DR. MEISEL: Okay. Thank you.

DR. SMITH: Dr. Nason, I'll come back to you. I think you didn't get a chance to finish.

DR. CHONG: [Off mic]. I'm sorry. I also wanted to respond to Dr. Meisel's question. So, while for insulin products that's not the case, there are some products where there is what's considered to be a titration dose. And it's an early dose that is not believed to be effective and it's only to be used temporarily.

DR. GUETTIER: I think, for some of these products, at least what you saw is the blackened area where you can actually dial up to doses that are not approved. I think, for the products where you can actually dial up the dose, usually that

blackened area doesn't include a unit or a dose.

DR. NASON: Thanks. I guess I was a little bit too slow last time to just get one or two more questions in quickly.

So going back for just a moment to the question about the injection site reactions by antibody, I was just wondering if you'd looked at that for the anaphylaxis as well, if you'd looked at that by antibody status.

Just so that I don't pause too long and miss my chance to ask one more question, also about the adverse events that were listed as early time frame in the iGlarLixi, I was wondering what time frame that was. It says iGlarLixi below 10 micrograms, but it doesn't specify what time window that was.

DR. CHONG: So I can answer the second question first. So that time frame that was presented was for up to 42 days. That was intended to reflect the range of lixisenatide between 5 and 10 micrograms.

Looking at earlier time points, a similar relationship is seen where the iGlarLixi event

incidence rate for the adverse effects are essentially in between lixisenatide and insulin glargine.

DR. NASON: Sorry, just so I understand, that's up to 42 days for people in all three groups?

DR. CHONG: Yes.

DR. NASON: And then if they're in the iGlarLixi, if they've gone over 10 during that 42 days, would they still be counted in there?

DR. CHONG: So we based that analysis looking at mean. So yes, there could have been people who were on iGlarLixi above that dose.

DR. NASON: Thank you.

DR. BALAKRISHNAN: Backup slide number 36.

DR. BONNER: [Inaudible - off mic]. I'm sorry. The name of the presentation, please.

DR. SMITH: So while you look for that slide, Dr. Everett, do you have a question? Let's move to that and then we'll come back. I'm sorry for the confusion on that, but for time, let's do that.

Dr. Everett?

DR. EVERETT: This may be something that requires the sponsor to look into their data and get back after lunch, is why I think I wanted to ask it beforehand. I'm looking at the primary endpoint slide for study 405, same for study 404, that's number 54, looking at the trend in hemoglobin A1c from randomization.

I would like to see the same slide with fasting glucose, morning glucose, a similar expression and representation because I think there has been some question about the titration algorithm and how aggressive it is in one arm versus the other.

Having some appreciation for what the achieved fasting plasma glucoses were in the, in this case, Lantus versus iGlarLixi would be helpful. It would be great if you had it for 404, too. Thanks.

DR. SMITH: Okay, it looks like that's clear. Again, while we're waiting, I'd like to ask if any panel members have questions that may lead

to a need to pull some data together and that we might want to look at later this afternoon. I'd like to kind of prioritize those. Yes, Dr. Reed, you have a question like that?

DR. REED: Sorry, I didn't hear you.

DR. SMITH: This would be a question that would require some work that would pull some data together for later this afternoon. Otherwise, I'm going to defer those until we get to those.

DR. REED: Okay. One may be, I'm unclear about how nausea was evaluated. And when you look at the differential of the adverse reaction of the combo to the monotherapy, the major difference in side effects other than allergy seems to be nausea. But it didn't lead to any discontinuation of therapy. And I didn't know if nausea was looked at in severity, was graded in severity in any way. And that may be more for the sponsor.

And then the second -- and that may be more for the sponsor. The other thing would be, is there any better data on this slide number --

DR. SMITH: Let's deal with the other one

first. Let's do one at a time.

DR. REED: I'm sorry.

DR. SMITH: So just if you're directing that to the sponsor --

DR. REED: I don't know that. Does the agency have that or does the sponsor? As part of their study design, did the patients grade their severity of nausea?

DR. SMITH: So yes, I would like the sponsor to answer that.

DR. GUETTIER: Commonly captured --

DR. SMITH: Then your other question, Dr. Reed?

DR. REED: On Dr. Balakrishnan's secondary endpoint slide set, slide number 6 on the secondary endpoints and the post-prandial glucose, it appears that, at day 28, there's an attenuation, as you noted, over time during the day that it's having less of an effect on the post-prandial.

One, is there any data beyond week 28? And is there any data that looked at antibody? You know, is this allergic, where the antibodies may be

binding active component and we may see a further attenuation out?

DR. GUETTIER: So let me just clarify this slide that was shown. Actually, the baseline is before people get any therapy.

DR. REED: Correct.

DR. GUETTIER: And then the only thing that you're actually looking at is the 28 day data. So that, you know, basically what you're seeing at baseline before you get any therapy is the baseline PPG that you're going to get. After 28 days of therapy, you see a reduction in the post-prandial glucose, predominately in the first meal. And then there's an overlap between the baseline.

DR. REED: Exactly. And could you explain what theoretical time on the X axis means? Am I reading that correctly? It's a little too small for my glasses.

DR. CHONG: So basically that is time from the dose.

DR. REED: So it's not theoretical. It's the actual time. The dose was given prior to

breakfast, is my understanding.

DR. CHONG: Yes, but I think using theoretical time means referring not to actual clock time. I'm sorry for the confusion.

DR. REED: Okay. Thank you.

DR. CHONG: And as to the earlier response, I'm not aware of it. I don't believe there's any data beyond 28 days looking at this sort of a trend or looking at it in relationship to antibodies.

DR. SMITH: Specifically questions that might require pulling together some data -- Dr. Seely, you had a question in this direction?

DR. SEELY: I had a question for the sponsor. Given the concern that the cap in the glargine titratability may have affected results, did you show and did I miss it or do you have the data on what percent of patients who received pen B were at the max dose at the end of the study?

DR. CHEW: (Off mic.)

DR. SEELY: Okay.

DR. SMITH: And Dr. Wilson, did you have a question of the same nature?

DR. WILSON: I'd like to know more about the more severe allergic reactions and the time course number one, why there's an apparent difference between the FDA's estimate -- on FDA slide 32, they showed that -- and the sponsor's estimate.

Then the other personal question, most diabetic patients are on either an ACE or an ARB, and those are highly associated with allergic reactions, whether there's any cross-over at all, any signal, because, as clinicians, we'd like to know that in advance.

DR. CHIN: So I'm going to take the question about the allergic reactions. My name is Stacy Chin. I'm a medical officer and allergist in the Division of Pulmonary Allergy and Rheumatology Products here at the FDA.

We were consulted to analyze and evaluate the results from the lixisenatide clinical trial program and the allergic reactions that were viewed by the ARAC committee. And largely, we agreed with the results of ARAC. The differences in our results and with what the sponsor presented mainly

come down to the application I think of the NIAID Sampson criteria.

So there are three different criteria that can be used to identify anaphylaxis and we traditionally use the more conservative criteria that requires presence of skin or mucosal findings or symptoms, along with respiratory and/or organ symptoms. The other two criteria that could be used allow presence of GI symptoms or, in the known exposure to an allergen, just hypotension or cardiovascular collapse.

So in our opinion, we came up with 8 cases, which were pretty close to what the ARAC adjudication committee came up with. But we consider all cases of anaphylaxis to be severe and potentially life-threatening because of its multi-organ system involvement, its unpredictable nature.

I think what the sponsor presented is, they eliminated some of the cases to, I guess, just present four that they considered more severe. But we consider all of the cases severe that meet the

Sampson criteria. Does that answer your question?

DR. WILSON: It does. But also I think it would be of great interest whether we should be especially vigilant, for instance the first 30 or 40 days, something like that, for starting patients on this product. And so the time course --

DR. SMITH: And we're going to revisit that this afternoon. We have somebody coming.

DR. WILSON: And the other issue, I already asked.

DR. SMITH: Yes, so we'll see those data this afternoon. So I'm now going to start the lunch break. And we'll have an opportunity for some more clarifying questions later afterwards. So we'll reconvene in this room again and we're going to start. I'm going to keep us on schedule by slightly shortening the lunch break.

DR. GUETTIER: I think the sponsor has pens available for people who actually want to look at the device.

DR. SMITH: Pens available. And we're slightly shortening the lunch break, which means

that we're going to start, according to the written agenda, we'll be back here at 1:05 for the open public hearing.

Please take any personal belongings you may want with you at this time. Committee members, please remember there should be no discussion of the meeting during lunch among yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:18 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:07 p.m.)

Open Public Hearing

DR. SMITH: So I'd like to welcome people back for the open public hearing session.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

For example, this financial information may include the sponsor's payment of your travel,

lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please only speak when recognized by the chairperson. Thank you for your

cooperation.

Will speaker number 1 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. CUNNINGHAM: My name is Gloria Gold Cunningham. I'm not representing any company. I participated in the diabetes study for insulin injections. I started in October 2014 in Los Angeles. I'm here today to speak on my experience concerning the medication mixture. I am being sponsored for my travel in order for me to make this trip.

I want to express the importance for me coming here today to speak. I cut my trip short from visiting my family in a celebration of my sister's 60th birthday party, and visiting my father and 7 other siblings to be here today.

Because I am a diabetic, this is an honor to speak on my experience with this medication because it really worked for me. I would like to continue to use this so I hope it's going to be offered to

the public.

Currently, I am on two insulin medications and it would be easier if I can use one insulin injection. I've been a diabetic for over 17 years, and, while taking this medication mixture, it has helped to control my A1c and glucose testing. Prior to participating in this study, my glucose was not being controlled.

Before I started the study, I had to be evaluated and tested to make sure I was a good candidate. At that time, I was ready to try anything to get my glucose under control. Just thinking about my cousin, whose glucose wasn't controlled, she ended up losing her leg.

During this study, I was told I would be using a new pen, which I did. I didn't notice any differences between this new mixture and the original. I felt fine and my glucose continued to stay at a normal range.

The only side effects were decreased appetite and weight loss. In my case, that was an added bonus. I didn't have any redness at the

injection site, not itching. It wasn't painful. And I didn't even feel a pinch.

There were no interruptions to my lifestyle while taking this insulin injection. What I liked best about this insulin is that I stopped having low glucose during the morning testing. My primary doctor was aware that I took part of this study and was pleased with my result, and so was I.

Currently, in April, at my last doctor's visit, my lab work showed that my A1c was at 8.1. During the study, it was around 7.0 or less. I followed back on the last few results. I realized it was because of the medication mixture I was using during the study.

At this time I am taking 2 injections and it would be easier if I can only use 1. It would be great if this medication is available. I would be one of your first patients to use it. Thank you for allowing me to share my experiences.

DR. SMITH: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you may

be representing for the record.

MS. VALENTINE: Hi. I'm Virginia Valentine. I'm an advanced practice nurse specializing in diabetes from Albuquerque, New Mexico. I'm here representing myself and people with diabetes. And diaTribe Foundation paid for my travel expenses.

I have been practicing caring for people with diabetes for around 35 years and I have cared for about 18,000 people with diabetes over my career. And I also have had diabetes myself, type 2 diabetes, for 35 years. I know you're thinking, gosh, she must have been young. I was. And I've tried everything. I've tried every diabetes medication that's available, although I never inhaled insulin.

(Laughter.)

MS. VALENTINE: I wanted to share with you, in about 2002, I started on a weight loss journey because I weighed 80 pounds more than I do now because of being on a whole lot of insulin. That's what we had then. And with determination and some really good drugs, like Symlin and Byetta, I lost

100 pounds over a 5.5 year period.

So GLP-1s are a life saver for me. I consider them to be one of the greatest classes of meds that we've ever come up with. Diabetes is complex. It's multifactorial, genetic, metabolic disarray. And unfortunately, it brings a constant struggle with weight. People with diabetes are blamed and shamed. We're told, just lose weight, and we wish it was that easy.

In America today, we treat type 2 diabetes as if it were a character flaw and it's not. We need a therapy without the struggle of additional weight gain. And we need things that are effective.

Lifestyle and metformin work initially for most, but for most, they're going to need additional therapies. And for many people with type 2 diabetes, it's going to be insulin. But insulin has a dark side and that is hypoglycemia and weight gain. And anything we can do to mitigate those risks with increasing efficacy, we need to make available.

Our providers, primary care providers, are overwhelmed with the complexity of the disease and trying to get people in control, trying to convince them to take an injection. And they need something that's simple to titrate that they feel that patients will actually take.

So this is the next big thing. A combination of insulin and GLP-1, I think, is the next big thing. I think it brings with it efficacy. It mitigates hypoglycemia and weight gain risk. And I implore you to act on this favorably today. Thank you.

DR. SMITH: Thank you. Will speaker number 3 please step to the microphone? Identify yourself. Please provide your name and any organization you are representing for the record.

DR. SCHWARTZ: Stanley Schwartz, a practitioner out of Philadelphia, emeritus from University of Pennsylvania, representing AACE. As you can see on the first slide, we're interested and committed to enhancing the ability of our members in providing the highest quality of patient

care.

In this regard, we believe that the more tools that physicians and patients have to treat diabetes, the better off the patients can be.

In the context of this, the two drugs we're talking about today, we believe lixi has another GLP-1. It has the glycemic benefit. It has the weight loss benefit, particularly the sugar store. The post-prandial glucose seems very important. And at a minimum, therefore, it may just offer competition that would help potentially reduce cost.

From the combination point of view, basal insulin with GLP-1, the single most important thing is it has the potential of avoiding the need for bolus insulin, avoiding three more shots a day, avoiding hypoglycemia and undue weight. So we might be able to get the patient to goal with less medications, in this regard reducing medication burden.

That fits with the AACE principles emphasized here. We want to get the lowest

glycemic levels we can without hypoglycemia, without weight gain, ideally with some weight loss. And we're going to use the least number of agents necessary to treat the most number of mechanisms of hyperglycemia. GLP-1 agents, by the way, treat about eight mechanisms of hyperglycemia.

They do this in an individualized way. So FDA and the sponsor provide information on the tools and then we have to, as individual clinicians, apply it to our patients. And in regards to hyperglycemia, we know it has adverse events. We know patients don't always feel these hyperglycemic events, which makes it even more critical in its importance of avoiding hyperglycemia.

By the way, there's a required hyperinsulinemic effect of all injected insulin products and hyperinsulinemia has many detrimental issues. So that translates in the AACE guidelines of not using early insulin. Lixi would fit in among any of the agents that are considered as first-, second-, or third-line in this regard.

But the committees yesterday and today were trying to figure out, where is this going to fit.

Think about it. 40, 50, 60 percent of our patients are on 1, 2, 3, 4 drugs, not getting to goal. That's when we would add this eight. Had there not been a GLP-1, these people with combinations of metformin, SGLT-2, DPP-4s, whatever, are people who are going to use this drug and that's a huge number of patients.

If they're already on GLP-1, then we would tell you add basal and, when you figure out the final dose, then you can make it easier for the patient by combining the shots into one product.

If they're already on insulin and you're going to add GLP-1, there's many ways to do that. Again, the simplest might be to add the GLP-1 in addition to the basal and then, by the way, use the combination product later on.

So AACE does not advocate for approval of any specific drug. There's a great need for new drugs to help manage the ever-increasing burden of type 2 diabetes. We need more effective

medications to improve glycemic control without the risk of hypoglycemia and weight gain.

I thank you for your time and consideration.

DR. SMITH: Thank you. Will speaker number 4 please come to the podium and identify yourself? Please state your name and any organization you are representing.

MS. COLLAZO: Thank you. Good afternoon. My name is Liz Collazo. I'm a person with diabetes, and a freelance writer, and blogger at the Angry Type 2 Diabetic, which reaches hundreds of thousands of readers every day. I'm here from the great state of Iowa and my travel arrangements have been graciously provided by the diaTribe Foundation.

I'm here today not just as a person with diabetes, but as the daughter of a person with diabetes and the wife of a person with diabetes. I speak with you with much anxiety today, but probably not as much anxiety as a person with diabetes has felt at being denied better tools to manage their diabetes.

Yes, it is true that some of us have felt anxiety at even beginning some medications. But often that anxiety does not happen in a vacuum. Many clinicians feel at odds prescribing persons with diabetes with better tools for management, tools such as insulin.

Just this last week, I got to experience some of that anxiety firsthand. I became very ill with a gastrointestinal virus and I had to attend the ER. At that point in time, a person like myself who strives to keep her blood sugar levels at below 140 milligrams per deciliter experienced blood sugar levels above 300 milligrams per deciliter. At all the stages of my treatment, staff refused to bring my blood sugar levels to normal control.

This is a very anxiety-producing situation for a person like myself. And I can understand the hesitance of clinicians to provide insulin as a form of treatment to people in my position, but I am not the exception. At doctors' offices every day, I am the rule to the situation. Clinicians

every day seek to deny people that need better management tools access to insulin or other medications that will more conveniently bring them to stabilized blood glucose control.

It is understandable, like I said before. There is potential for errors, resulting in hypoglycemia and perhaps resulting in liability. There is also the potential of upsetting the apple cart of diabetes management and a person's routine by bringing in weight gain and added costs of co-pays.

But these concerns aside, people with diabetes still need better management tools. They still need access to these tools. And a GLP agonist and basal insulin combination would help not just alleviate some of those potential patient concerns, but it would also help reluctant clinicians empower people with actual access to tools for better management of their diabetes.

Patients need more tools that they can actually take advantage of in order to manage their conditions to their individual health needs and

concerns. And the FDA has some real opportunity and power today to put some of that power and some of that initiative in the patients' hands to bring their diabetes under control today.

I urge you to take those steps to help persons like myself, my husband and my late father, who passed away, from having fears, reluctant clinicians, and no access to better management tools so that they can stay alive for more years for their families. Thank you very much for your time.

DR. SMITH: Thank you. Will speaker number 5 please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SUSSMAN: Good afternoon. My name is Glen Sussman. I am the founder and lead investigator at ICCT Research International in Chicago, which I founded in 1994. We've done approximately 200 trials. The vast majority are diabetes since that time.

I was involved in one of the many Sanofi

trials. In this case, in the interest of disclosure, I am not being compensated, only the pre-arranged travel expenses, nor do I hold any financial interest in the outcome of this study, or any others.

In this particular study that I'm here to address, we had a population base as we normally do. Our base is primarily Latino, primarily Spanish speaking in Chicago. There is a problem in the Hispanic, particularly the immigrant Mexican community, with the use of injectables. There are fears and concerns and we have to get them over the hump. And the difference in using a pen device, as we did in this, as opposed to the old fashioned vial and syringe is significant.

In this study, we enrolled 4 patients. One of the patients was a Caucasian, non-Hispanic Caucasian male who screen failed initially because of an A1c above inclusion criteria. Another was a 22-year-old Latino male who made it through the first 7 visits. We had switched him from Novolin to Lantus per protocol. At that point, his A1c

dropped from 8.6 to 6.7. He was excluded.

Two other patients remained, one a 63-year-old non-Hispanic female who was ultimately randomized to lixi. She did very, very well during the course of the study. She had no study specific or product specific AEs at all.

She had just a couple of adverse events which were historical in nature. She had a couple of nocturnal hypo events and that's to be expected of virtually all diabetics. We deemed it to be due to family stress and to some occasional dietary non-compliance, not to the study or the study drug.

Another lady was a 44-year-old Mexican-American, non-English speaker, who was randomized to Apidra. Her A1c also went down significantly. She had a couple of AEs, again strictly historical, neuropathy for one, occasional neuropathy, all moderate. She had some insomnia and an occasional UTI, not unexpected in this population, again, not attributable to study drug. All were historical.

I found that during the course of this

study, by the use of GLP-1s in conjunction with -- we had this experience with the GLPs anyway. We found that it was most effective. There were no problems whatsoever with the device.

There was one small glitch during the course of the study, which was patient oriented. She had twisted the top. The dosing is much better obviously with a pen than it is with a syringe and vial. She had twisted it a little bit too tightly. She brought it in. My coordinator fixed it. Never had another problem.

There was no problem whatsoever. I sat in on part of your human factors presentation. There was no problem in our office on mixing up the two different pens. They were clearly marked. There was no incidence whatsoever of patients taking the wrong pen, of overdosing.

The product, in our experience, works very, very well. I happen to be an advocate of replacing the sulfonylureas with GLP-1s. There might be some disagreement on that. In the long term with the GLP-1s, we get, of course, the weight loss, but we

also get virtually no hypo events. Metformin, of course, has its problems.

In this case, we were very happy with the study. If it can be brought about that it's done in a single pen, the compliance rate will go through the roof. So that there's one injection a day. My goodness, we'd have phenomenal compliance and therefore great results.

I want to stress the issue of once a day. I want to stress the issue of the lixi being quite effective in our experience and we've done a number of studies. And we were overall very satisfied.

I have nothing else to say that's not on my notes. So I thank you for your time and will terminate now before my light goes off.

DR. SMITH: Thank you. Will speaker number 6 now please step to the podium and introduce yourself? Please state your name and any organization you are representing.

MS. PARRINO: Hello. My name is Maria Parrino, and I am from no organization. I would like to state though that my travel expenses were

paid by Sanofi.

I was diagnosed with type 2 diabetes in 2005, even though there was no diabetes in my family. Since that time, I've been continually on metformin at gradually increasing doses until, now, I am at the maximum dose of 2,000 milligrams a day.

During those years, when metformin no longer met my numbers where they should be, I took either medication such as Actos, Januvia, et cetera, many medications. With those, for one reason or another, whether it was the expense or the meds were not working to justify the expense, it was on to another medication.

My doctor recommended insulin, because, as he put it, insulin is what your body needs, not pills. I always declined because I was leery of the injection part and the stigma of being insulin-dependent. Just the thought of injecting myself made me ill. It was the same reaction I had when my optometrist recommended contact lenses. The thought of putting something in my eye was not good. I eventually took a shot and I have not

regretted it since.

In May of 2014, my doctor asked if I would join a clinical trial for an injectable drug. I thought this would be a good time to try injections, as it was only for a few months. And let me point out that I greatly dislike pills, especially metformin, because the pills are like horse pills. However, during this trial, I did stay on metformin.

I remember being taught the procedure for the trial by the PI. Injecting it was tricky. But it was not confusing, it was just different. And it takes longer to take an injection than it does a pill. I believe I did well on this drug. My numbers were good most of the time. I had no side effects, which was great.

I even lost some weight, about 10 to 12 pounds. However, in March of that year, we rescued a 2-year-old German Shepherd and he loves to walk. And so we walk him at least 45 minutes every evening and, with a dog that large, you don't stroll. Therefore, I can't say if the weight loss

was a result of walking or the medication.

Overall, I had a very, very good experience on this drug. I hope it comes on the market soon and I will take it again. Thank you.

DR. SMITH: Thank you. Will speaker number 7 please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. CLOSE: Hi, my name is Kelly Close and thank you so much for the chance to speak with you again today. I'm the founder of the diatribe Foundation, which is a non-profit focused on improving lives of people with diabetes and pre-diabetes. And I've had diabetes myself since 1986.

By way of disclosure, our biggest funder at the diaTribe Foundation is the Helmsley Charitable Trust. We're also supported by multiple patients, families, not-for-profit and for-profit organizations, including today's sponsor. I also founded Close Concerns, a healthcare information company focused exclusively on making people

smarter about diabetes and obesity. The sponsor is also one of several hundreds of subscribers to a news service that we started in 2007.

The number one message today is that giving people with diabetes and their healthcare providers more tools to be successful could greatly improve lives and outcomes. And, you know, so just a couple of big-picture points before I talk about the rest of the things on this slide.

So one of the other things that I had talked about yesterday was that I don't think necessarily so many patients out there realize how underresourced the FDA is. I want to say thank you for all that you do.

I think, similarly, just as we don't realize how much work you have, I think, as patients, we also don't realize how much work all of our doctors and nurses have. And there are countries like the U.K. where, as I understand it, doctors and nurses who are in different specialties are actually paid the same. They make the same salary.

This is not true in the U.S. Really,

treating people with diabetes is a labor of love. So many of you do it. Thank you. Given all of the increased administrative responsibilities, we as patients really want doctors and nurses, patients, partners, parents, anyone involved with patients to feel like they can be successful.

Again, big picture, I'm lucky I'm in a position where I speak to a lot of doctors and nurses all through the course of the year. I have never seen a time when they are more exhausted and when they are more overwhelmed. And this is unsolicited. I mean, I don't know that they would even necessarily like me saying that, but that's my impression as a patient and I'm really worried about that.

I think that, as we then think about the therapies that take the longest time to prescribe and learn how to teach, we should become increasingly concerned because there is less time to do that. So I did talk a little bit yesterday about how mealtime insulin in particular is the most intensive therapy to teach. That fits

increasingly poorly into the current system because healthcare provider time is getting more and more limited.

As I've heard Dr. Ratner of the ADA say so many times, our system is just exploding. It's not so much that every single person costs so much more, but there are just so many more people coming in. We want to make sure that patients, especially with type 2 diabetes, which is a progressive disease, can do well at every single point along their journey.

So as much as we can do to keep people on easier, simpler therapies that they can be successful on, the better that they will be, just because there are more and more and more people out there. The number of people has gone like this and the number of interest, the amount of interest in the area is really neutral or going down.

Some of that is due to paperwork that doctors have to go through. I think some of it is also really due to a really great understanding that I think we're getting to, which is that we

need to pay way more attention to mental health. We need to pay more attention to not just clinical depression. That's really important. We know people with diabetes suffer more from that.

But we also know that we need to pay more attention to just stress and to emotional wellbeing. And I'm so happy to see the healthcare provider community doing that, but that time does have to come from somewhere. And so that's another reason why it's really important to get so more and more alternatives that are easy and to keep people healthy.

It was also really interesting for me to listen yesterday to hear some of you talking about how complex it seemed, a therapy like the ones that we're talking about today and yesterday. If you know how complicated mealtime insulin can be, this is like a cakewalk.

So I'm really, I'm grateful that you're worried about like the 2:1 versus 3:1 and can we understand that, et cetera, but mealtime insulin is actually far, far, far more complicated than that.

And I just don't actually hear a lot of people worried about that from a patient's perspective.

So we really do see this increasingly challenging American healthcare system severely limiting the healthcare provider time, like I said, the ability to prescribe and titrate multiple drugs. And so, by offering a simpler way to use a GLP-1 agonist and insulin, iGlarLixi really addresses both of those problems.

I'm going to go through these really quickly. We know there are multiple problems that make that event therapy challenging.

DR. SMITH: Yes, we're short on time, so you should try to wrap it up pretty quickly.

MS. CLOSE: Absolutely. I just want to say again, thank you for considering the new therapies and thank you for considering, as the American healthcare system evolves, what we need as patients and as healthcare providers. Thank you.

DR. SMITH: Thank you. Will speaker number 8 now please step up to the podium and introduce yourself? Please state your name and any

organization you are representing.

DR. RATNER: Good afternoon. I'm Robert Ratner, Chief Scientific and Medical Officer for the American Diabetes Association, which represents over 15,000 professional members and almost 30 million Americans with diabetes. I have no financial conflicts, although 5 years ago I ended my involvement in the clinical trials of iGlarLixi, which we always used to call LixiLan, and also of IDegLira.

Although the American Diabetes Association does not testify in support of individual products, we strongly support the need for further research and improved therapies for the treatment of diabetes as an unmet need. I spoke to you yesterday about those unmet needs. I'm not going to repeat myself.

However I've been very gratified in listening to the agency, to the sponsor, and even to the members of this committee about the importance of our standards of care and how our standards of care can and may be able to influence

the utilization of medications in the U.S.

As I listened to the discussion yesterday, many of the issues related to questions 1 and 2 yesterday or questions 2 and 3 today are actually in our standards of care. So what I wanted to do today was actually help you out a bit with what our current standards say about how and when to use medications.

The issue of combination medications comes into play by an intensive review of the data on add-on therapies among all of the different medications that are in our armamentarium.

When you begin to look at that data, what one finds is that the addition of one medication over another or de novo medication results in approximately a 0.5 to a 1.1 percent fall in hemoglobin A1c. It's a limited response. It's uniform with virtually all medications that we've looked at. Some are a bit more potent than others, and some are clearly less so.

So the recommendations that go beyond the table that Dr. Wilson used yesterday goes into

very, very simple descriptions. For all patients considering initiating therapy with a dual combination when hemoglobin A1c is greater than 9 percent to more expeditiously achieve the target A1c level, insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if symptoms are present or any catabolic features are present.

Consider initiating combination insulin injectable therapy when glucose is greater than 300 milligrams per deciliter, or A1cs greater than 10 percent. As the patient's glucose toxicity resolves, the regimen may potentially be simplified. We have a standard of care that says when combination therapy should be initiated.

The other issue is that, when you begin to look at our therapeutic options in type 2 diabetes, it's been shown by the sponsor today, it was shown consistently yesterday, what you see is a variety of different drugs that are available. What wasn't

in those abridged versions is that we introduce choice and shared decision-making as to which medication actually gets used.

So when you begin to look at what we now consider a very famous table, what you find are characteristics of each of those drug groups and how they should be used.

This includes efficacy, hypoglycemia risk, weight, side effect, and costs. All of these are discussed with the patient in order to determine what the best way is of approaching their particular disease.

The other comment that was made yesterday was, do we really know what the impact is of adding a GLP-1 to insulin or insulin to GLP-1 in a non-fixed-dose regimen. And the answer is, we do. We have published papers, one by John Buse in the Annals of Internal Medicine, adding exenatide to insulin. We have another adding insulin to GLP-1, and that's by Hans de Vries in Diabetes Care.

These data demonstrate what the change in insulin can be when it's uncapped and it's 7 units.

That's the change from baseline in the Buse study, 7 units. When you begin to look at who is being treated, just to give you an idea, in the Buse study, the average weight was 95 kilos and the average dose of insulin was 49 units. We have the data to answer many of the questions that you have. Thank you.

DR. SMITH: Thank you. Will speaker number 9 please step to the microphone and introduce yourself? Please state your name and any organization you are representing for the record.

MS. REGIER: Good afternoon, and thank you so much for the opportunity to speak again. My name is Emily Regier, and I am here representing Close Concerns, a healthcare information company that aims to improve patient outcomes by making everyone smarter about diabetes and obesity.

We attend about 50 scientific and regulatory meetings each year and speak frequently with a wide range of leaders in the diabetes field. And on a personal note, I'm also here as an aspiring physician myself who is eager to continue learning

as much as I can about all of the advances in this field.

As far as disclosures go, as Kelly mentioned, almost 300 for-profit and non-profit organizations subscribe to our fee-based newsletter, Closer Look, including today's sponsor.

GLP-1 agonist basal insulin combinations have been a very frequent topic of discussion on the diabetes conference circuit over the past few years. And I hope again in this presentation to convey the level of excitement they have generated from speakers that we've heard.

By my rough count, we have reported on about 50 talks at 17 different meetings over the past three years that were at least partially focused on these drugs. And as we saw this morning, the data is compelling. This combination beat both of its components in terms of A1c reductions in a phase 3. It allowed 55 to 74 percent of participants to achieve their target and led to robust post-prandial glucose reductions.

Perhaps even more importantly for patients,

it comes with less weight gain, no additional hypoglycemia compared to basal insulin, less nausea compared to a GLP-1 agonist alone, and only one injection compared to the at least two per day that would be required with the two components separately or more for multiple daily injections of insulin.

It's also become clear that key opinion leaders see these combinations as extremely versatile. We've heard them described as the modern equivalent of basal plus therapy, a superior alternative to basal insulin or a GLP-1 agonist, logical to use early in the disease progression, and potentially even the best drug to use after metformin.

Dr. John Buse said he finds it hard to identify a population that would be ill-suited to treatment with these combinations for clinical reasons. Of course, this product will not be the right choice for every person with type 2 diabetes, but we do think it will be an appealing option for an unusually diverse range of people.

Finally, I want to close with just a few more testimonials from key opinion leaders on the conference circuit to reinforce the excitement we've heard around these drugs.

We've heard them described as a physiological choice that addresses both fasting and post-prandial glucose, which I think is particularly true for this combination, the most exciting area of current development for GLP-1 agonists. These combinations will prove to be very potent, the most effective way to treat type 2 diabetes bar none. And if I only get one shot on goal, I do think this is the single best shot we have, no pun intended.

So I'd encourage the advisory committee to again consider these opinions when making your decision. Thank you again for the opportunity to speak.

DR. SMITH: Thank you. Will speaker number 10 now please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. GAO: Hi. My name is Helen Gao and today I'm representing dQ&A, a diabetes market research company based in San Francisco. By way of disclosures, I am also representing Close Concerns, who paid for my flight here today. My colleague, Emily Regier, recently just reviewed our disclosures.

In my remarks, I will be referring to the fixed-ratio combination of iGlarLixi as LixiLan. Today I'd like to discuss the unmet need for therapies, like LixiLan, based on survey data for thousands of patients with diabetes. As many of you know, type 2 diabetes is a progressive disease that requires continual adjustment of medication classes and doses.

Most patients eventually require multiple daily insulin injections. These means these patients take 3 daily injections of mealtime insulin on top of a daily injection of basal insulin. So it's understandable then that many patients delay intensification to mealtime insulin, even when it's necessary for their health and well-

being.

In fact, a recent dQ&A survey of around 5,000 people with type 2 diabetes found that only 12 percent of patients who are on basal insulin had talked to their doctor about adding a mealtime insulin. Even among those with an A1c over 9 percent, only 22 percent had, had this conversation. This is especially troubling because these patients are at high risk of disabling and costly complications.

dQ&A also asked patients, diabetes educators, and physicians about their biggest concerns about adding a mealtime insulin therapy. The top 5 reasons they gave were; one, it will be more of a hassle, two, the difficulty of dosing insulin and counting carbs, three, the costs related to adding mealtime insulin therapy, four, the increased risk of hypoglycemia, and, five, the weight gain that's so often associated with insulin therapy.

LixiLan can address all of these concerns, making it an excellent option for millions of

people with type 2 diabetes who require insulin intensification. LixiLan will be one pen, one injection, and one prescription, so it will not increase the hassle factor on top of taking a daily basal insulin.

Similarly, patients who are on LixiLan will only take a single daily dose regardless of their carb intake. So this will avoid complicated dosing schemes.

In addition, patients on LixiLan will have a single prescription with one co-pay and I hope this would translate to lower out-of-pocket costs for these patients compared to filling multiple prescriptions with multiple co-pays that are associated with basal bolus therapy.

We also saw earlier that LixiLan doesn't increase hypoglycemia risk on top of what you would see with Lantus therapy. And this is really important because mealtime insulin is often associated with increased hypo risk in type 2 diabetes. Additionally, LixiLan does not cause weight gain, which is so often associated with

additional insulin therapy.

Furthermore, lixisenatide and LixiLan have unique advantages not offered by other GLP-1 agonists or GLP-1 agonist basal insulin combinations. As a short-acting GLP-1 agonist, lixisenatide has been shown to have a greater effect on post-meal glucose than GLP-1 agonist liraglutide when added to insulin glargine. Lixisenatide and LixiLan therefore would be ideal alternatives to mealtime insulin.

In summary, it is safe to say that LixiLan could be a game changer for type 2 diabetes. It addresses so many barriers to optimal diabetes care and can dramatically improve the outcomes and reduce the rate of complications in many patients with diabetes. This is a big win for cost savings to the system. It's also a really big win for patients.

People with diabetes are people before anything else and they're juggling a million different things that compete with diabetes management for their time, money, and energy.

LixiLan can lessen the burden of diabetes management for many of these patients and help them better fit that management into their daily lives. In doing so, it can improve both their health and their quality of life.

I sincerely hope the FDA will take the opportunity to approve LixiLan today and advance the health of millions of Americans with diabetes. Thank you.

DR. SMITH: Thank you. Will speaker number 11 please step up to the podium and introduce yourself? Please state your name and any organization you are representing.

MR. GARCIA: Hello. My name is David Garcia. I'm not representing any organizations, but I would like to thank the Sanofi drug company for sponsoring my trip to talk to you about my experience.

I'm a recently retired high school teacher. And whether the feeling that I had when I had diabetes not under control, I really didn't feel like I could continue teaching more than 30 years

of high school. But one of the things that my doctor said was, "Your A1c is pretty high," which was around 9 at the time when my doctor was very concerned, and so was I.

I just had a very bad feeling about myself. And again, maybe that's one of the reasons why I didn't complete my 30 years of high school, because I just wasn't feeling like I could do that kind of work anymore. I was running out of energy. I felt really down low.

So my primary physician then referred me to the Metabolic Research Center. So I went there. I went there at a weight of about 240 pounds, which I had with me for quite a while. And after the end glucose levels of 180, 190, that was fasting levels.

But after beginning the drug mixture, I soon started to feel a lot better. My energy was starting to come back. Not only that, but I also started to notice that my glucose levels were also coming down. My morning glucose levels were now down to 120.

By the end of the study, which was at about, it seemed to me, a year later, my glucose levels were down to 90 and I lost quite a bit of weight. I went down to 190. So from 240 to 190 was quite significant. The only disadvantage, too, is that I had to buy new clothing. But I felt really, really well.

One of the important reasons why I really wanted to come and speak to you is because, again, it gives us an option, an easy option, the medication. I mean, being a science teacher really doesn't give me the experience of knowing things about medicine, but this was a very simple medication to take, simple dose in the morning, simple calibration. I injected it.

As a matter of fact, I did it between first and second period, take my glucose levels, too, between breaks. And it was quite simple, so it was something that I was happy with.

I also noticed, too, that during the study I had numbness in my feet and the numbness seemed to also disappear. My feeling in my toes are back to

normal again. So overall, at the end of the studies, I felt fantastic and I wish I could now go back and teach high school again. But that's over with now. I don't think I want to go back to high school. But that was a very nice thing.

In conclusion though, I'd like to thank you, the committee, and Sanofi for allowing me to speak. I hope that you make this product available so that I can use it again.

I'd like to go back on it again because I'm starting to notice again my weight going back up. So my A1c levels, too, I haven't checked, but I've been afraid to even go to the labs to see what they're like now.

So I really hope that your product comes out soon and it's affordable. And it is easy to use. So thank you very much for giving me this opportunity to speak.

Clarifying Questions (continued)

DR. SMITH: Thank you. And thanks to all of the open public hearing speakers. The open public hearing portion of this meeting has now concluded

and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

Before moving to the specific questions from the FDA, I'd like to, as expeditiously as we can, resolve remaining questions about the data from the panel members. If we could start with slide 8 that Dr. Nason has requested earlier, perhaps we should address that first.

DR. BALAKRISHNAN: [Inaudible - off mic.]

DR. NASON: Yes, I think I've been looking at slide, gosh I can't even read what it is. The one that was talking about the antibody positive versus negative in terms of the --

DR. BALAKRISHNAN: In terms of injection site reactions or allergic reactions?

DR. NASON: Sorry. I'm having trouble switching back to where we were.

DR. SMITH: It's been a few hours. Do you want me to move on and if we --

DR. NASON: Yes, I don't think I can go back to it.

DR. SMITH: So we'll move on, then.

DR. BALAKRISHNAN: Yes. But can you show backup slide 36, please?

DR. SMITH: Backup slide 36.

DR. CHONG: Yes, that was the slide we had trouble pulling up.

DR. BALAKRISHNAN: You had asked about data on allergic reactions and antibody concentrations. [Inaudible - off mic]. Okay. Since it's taking time to come up, this is essentially the data from the sponsor.

Basically, in the placebo-controlled trials, there were about 17 subjects with allergic reactions related to the investigational product, which is a 0.6 percent of lixisenatide versus about 2 on placebo.

Then what you have on this slide here now is essentially the events that were in lixisenatide patients and placebo patients. So there was about 1.9 percent of patients on lixisenatide versus 1.1

on placebo.

It seems like it was more or less, you know -- because of the low number of events, you couldn't really say -- they didn't correlate much with ADA positive or ADA negative status. But as concentrations increased, the percent of hypersensitivity reactions in patients with positive antibody status did increase.

DR. CHEW: Dr. Smith?

DR. SMITH: Yes?

DR. CHEW: We have some comments from the sponsor on this information, on the ADAs and patient safety.

DR. SMITH: Sure. Why don't we move to that? Thank you.

DR. CHEW: I'm going to ask Dr. Newton to comment on the ADAs and the relation to efficacy, and Dr. Sharma on the relationship to safety.

DR. NEWTON: So could I have the slide on concentration relationship with efficacy first? Okay, this is a slide that actually shows the relationship of antibody status and antibody

concentration to efficacy. And a couple points in this slide.

A couple points in this slide, first of all, the antibody-positive status is about 70 percent of the population. But almost two-thirds of those antibody-positive patients are actually below the LLOQ of our assay. Remember, how you establish your assay can dictate the sensitivity of the positivity rate. So that's why it's very difficult to compare across products.

But the most important thing here is that is really only at the highest antibody concentrations are we seeing a diminishing of efficacy. It's around 2.4 percent of the population in total. And so the next question you'd ask is, does high antibody concentration actually predict efficacy?

This is this slide. This is the total number of patients and then we've got the A1c bracketed in different rates from the right-hand side, where there is little or no efficacy, to the left-hand side, where there is profound efficacy of the drug. And you can see that there is a high

concentration of antibody-positive patients with high concentrations with profound clinical benefit as well as intermediate scale concentrations.

DR. CHEW: Thank you, Dr. Newton.

DR. SMITH: Yes, Dr. Neaton had a follow-up question on that.

DR. NEATON: I think maybe Dr. Nason asked this. Can you just clarify when the antibody measurements were made?

DR. NEWTON: So I'm looking for the slide -- so we're taken at fixed, as somebody pointed out earlier, they're taken at fixed periods over the study.

DR. NEATON: So these are basically measurements that are taken during follow-up?

DR. NEWTON: Yes. During the study, so weeks 2, 4, 12, 24 and so on.

DR. NEATON: So which one are you using?

DR. NEWTON: We're using the highest value basically.

DR. NEATON: So you've classified people by the highest --

DR. NEWTON: Highest value.

DR. NEATON: -- of multiple values taken during follow up.

DR. NEWTON: Of highest value, exactly.

DR. NEATON: And essentially looking at their --

DR. NEWTON: Yes.

DR. NEATON: -- hemoglobin A1c response at 26 weeks.

DR. NEWTON: Yes.

DR. NEATON: So I mean, there's some issues there with what you're doing, I think, in terms of understanding that analysis.

DR. CHEW: What questions do you have on the analysis, Dr. Newton, that we can answer?

DR. NEATON: I don't know that you can answer them without a lot further analyses. I mean those groups are no longer comparable so who are you comparing? You're comparing against -- what's the control arm that you would compare these things against, these levels against? So this is just in the treatment group that you're looking at them?

DR. CHEW: That's right.

DR. NEATON: And so I'm trying to get an idea of a reference to understand, are there individuals that are, you know, for whom these antibodies are becoming elevated that are different that should somehow be taken into account in these analyses? Are there any confounding factors that were considered at all?

DR. CHEW: Well the analyses we've done show that --

DR. NEATON: Like duration of therapy.

DR. CHEW: Yes, that the high concentration of greater than 100 is -- there's a loss of efficacy in about 2.5 percent. But that's a small number and that it's not even absolutely predictive because patients who have an A1c reduction could also have a significant ADA concentration. So what we're saying is, it's not very clear, but the magnitude of the number of patients is small. And for a product that's titrated, that also could be managed.

DR. NEATON: So I mean, just a simple

question. Did people become -- before they became at high levels, they were intermediate levels or were not antibody positive. Was their hemoglobin A1c good then? Or did it basically change as a consequence of becoming antibody positive?

DR. CHEW: Dr. Newton, could you answer this question? I believe these were end-of-study A1cs.

DR. NEWTON: I don't believe we've looked at that relationship you're talking about.

DR. NEATON: [Off mic - inaudible]. I don't know what the [indiscernible].

DR. SMITH: So Dr. Guettier, a comment on this point?

DR. GUETTIER: Yes. I think you're struggling with a lot of the struggles that we have with these types of data. I mean, these are data that are derived during the trial. Most biologic products have to do this immunogenicity testing. And most biologic products have antibodies that are developed and then we have to sort of read the tea leaves. At least, if you have a good suggestion for how we should analyze these types of data, we'd

be interested in hearing it. It's not easy.

DR. NEATON: I mean, I can see that. I think at least I would take into account the time course of the hemoglobin A1c changes relative to when the antibodies went from negative to positive. And so that doesn't seem to have been done in the analysis we saw.

DR. CHEW: Yes. Clearly, this is an area that's very difficult to analyze because it takes a long time to settle on your A1c, 12 weeks. And then so antibodies are also going up and down, but it's a very small magnitude of number of patients who have that antibody and the reduction in efficacy is small.

Now, safety was also another question that we wanted to comment on for ADAs. Dr. Sharma?

DR. SHARMA: When we look at the anti-drug antibodies and the allergic reactions, again as Dr. Newton said, we're taking the anti-drug antibodies at specified time points and the allergic events can really occur at any time.

The slide that was shown previously looking

at all the allergic reactions, a point to consider, these were adjudicated allergic reactions, but this was allergic rhinitis that was included in there and other types of events they wouldn't have expected to be drug related.

When we looked at this question of the relationship to drug, we looked at those that were specifically adjudicated by our ARAC as drug related because we felt those might be the best ones to look at where we weren't looking at all that background noise.

So when we put the slide up, what you'll see here is that we had in the phase 3 placebo-controlled trials 17 patients who had drug related reactions. Of those, 15 had an ADA status that was available. And you see, when we look at the positives and the negatives, we're not seeing an association between drug-related allergic events and the status of being ADA positive.

DR. CHEW: Thank you, Dr. Smith.

DR. SMITH: So while we're on this topic, we had also asked for information on the temporal

pattern of allergic reactions.

DR. CHEW: Yes. I'll get Dr. Kaplan to come up, who is the chairman of our ARAC. Dr. Kaplan, could you come up?

DR. KAPLAN: Yes, good afternoon. I'm Allen Kaplan and I headed the adjudication committee that dealt with allergic reactions. And parenthetically, my specialty is in urticaria, angioedema, and anaphylaxis. And I started my career as head of allergy at the National Institutes of Health.

We used the Sampson criteria as a definition of anaphylaxis and that was because, in years gone by, it was sort of a colloquial definition that anaphylaxis is a bad allergic reaction, probably multi-systemic, and potentially fatal. And that for years and years was felt not to be adequate.

It really is a broad syndrome, and the Sampson committee, which I participated in at least some of their meetings, was created by the NIH to try to determine criteria that could be used to assist in the diagnosis.

That has been accepted and it's used all over the world now. And we applied it to these cases. Of course we looked at all allergies, and it was just one of the criteria as to whether it fulfilled criteria for anaphylaxis.

We also had a severity scale from 1 to 6, the 1 being the mildest and a 6 would be a fatality. And it is not an oxymoron, I want to point out, to have an anaphylactic reaction that is considered not particularly serious. That's against the grain unless you're an allergist and are familiar with this.

But we had 11 adjudicated cases that we thought fulfilled the criteria of anaphylaxis by those criteria that were due to the drug. The denominator was in round figures 9,000 and you saw that earlier.

We had divided those 11 into 4 that were, quote, severe if you will, leaving 7 that were not. And let me explain what I mean by that. A level 1, for example, was an individual who was treated with an antihistamine, was observed for a while, and

went home.

There were a number of people who had hives. If they had vomiting with it or let's say cramps and a diarrheal episode and were treated in that way and went home, that was considered anaphylaxis because it's two systems, skin and GI. Now, there was no way that person is at risk of a fatality at that point in time and the person was treated by the person administering the -- who they had seen for the medication, and so there was not necessarily a specialist in this.

Seven people were either a grade 1 or 2. They were treated with an antihistamine. Or if they made a 2, they got steroid or epinephrine, were observed, and went home.

The four that were more severe, were the more standard anaphylactic that either had a respiratory component or were hypotensive, and we pointed those out to you. Three of them had hypotension. They didn't pass out, but they had hypotension like 90/50, went to an emergency room, was treated, observed and 3 out of the 4 fulfilled

that.

Then there was that one case that we all wrestled with because the individual received the drug and reacted to it at the very inception. There was no past history. They hadn't encountered a GLP-1 agonist previously. And that was called anaphylactoid, anaphylactic-like, or even idiosyncratic. We could not explain it and it did not fulfill the usual immune reaction.

So that's what we adjudicated in terms of the anaphylaxis. You may recall for one of the slides Dr. Sharma showed you that, in terms of allergies per se, lixi and exenatide were roughly the same, and dulaglutide was three times more. And so that's the predilection for allergy.

DR. SMITH: So what we really want to know --

DR. KAPLAN: -- for allergy --

DR. SMITH: Excuse me. What we really want to -- this is very helpful, but what we're really looking -- and for time I want to move this along -- we're looking at the temporal pattern of

occurrence of these events.

DR. KAPLAN: Temporal pattern. Okay, we have that. We have that slide.

DR. SMITH: We can see the Kaplan-Meier plot, okay.

DR. KAPLAN: Yes, most of the --

DR. CHEW: Yes, we do have that. We have a slide. They'll show it. There we go. So you can see most of the cases occurred within the first few weeks, 2 or 3 weeks, half of them. That was about the 50 percent point. And as Dr. Kaplan said, none of these cases was fatal. The most common cause is urticaria.

DR. SMITH: I think, Dr. Wilson, you had a question related to this?

DR. WILSON: Yes, so that's very helpful. And I think the question we have is as a physician who would be prescribing this. We'd like to know if somebody's had, for instance a bee sting problem or --

DR. SMITH: Can we keep the slide up, please?

DR. WILSON: -- or another -- some other event that has caused anaphylaxis or urticaria, or angioedema, requiring either an epinephrine kit or an oral medication. In the first month, should they have that around, so to speak, to ensure safety? That's the question.

DR. CHEW: Are you saying is there a relationship between bee-sting allergy and --

DR. WILSON: I'm just saying a previous history of angioedema or anaphylaxis in any shape or form. For instance, many of us have relatives who have had this and I say, if you're going to start this medication, should we be alerted that those people are at greater risk? That's the simple question.

DR. CHEW: Again, Dr. Kaplan, you looked at the risk factors for these.

DR. SMITH: So what I see on this slide is that it looks like it's about 60 percent occurred within the first 6 weeks or 7 weeks. It's a little compressed on that end, but that's what I'm seeing on this slide.

So it looks like there's then a continuation at a fairly steady rate over a period of a year. So this is one set of numbers. It doesn't mean that would play out. But it looks like about 60 percent occur within the first 6 or 7 weeks. So not surprisingly, it's not intensively compressed early.

DR. CHEW: There was the relationship between previous history of anaphylaxis.

DR. KAPLAN: Anaphylaxis of the sort that you alluded to is very specific. If somebody has insect-sting anaphylaxis, they have no more chance of having an anaphylaxis to this than I would, who is not taking either.

If you had a person who had a chronic disease with recurrent angioedema, where it becomes almost impossible to interpret the particular episode as to whether they had an underlying condition or something new you've done, those would be the exceptional people where they may carry one anyway, but in general not, because it's quite specific and it is not predictive.

That curve, for at least an incidence of going up early in the time that you're taking the drug, is typical. Right? We all know it takes a couple of shots to become sensitized and then you might have a reaction if you're going to have one at all, although it can be ongoing with time.

DR. SMITH: Sir, it seems the summary would be the numbers as I kind of summarize them, in that there aren't otherwise predictors that occur in advance.

DR. KAPLAN: That is correct.

DR. SMITH: Okay. Are there other questions that were asked in which we asked for more data?

DR. CHEW: Would you like me to go through them quickly?

DR. SMITH: That's what I would like, yes.

DR. GUETTIER: Dr. Smith, could we clarify a point that was made by the sponsor? So I think the consultant actually stated something that we think is factually incorrect, which is a comparison of this program to the dulaglutide, saying that, in the dulaglutide application, there were more

allergic reactions. We actually reviewed both programs and Dr. Balakrishnan has slide 34 as a backup slide to actually comment on that.

The other thing is that, at least from our review, these are product-related adverse reactions. And the way that we determine that they're product related is we go through a causal association type of narrative review. So for all these cases, we felt that we had excluded other potential risks, that the events occurred in close relationship to the taking of the drug. And so we do believe that the risk that Dr. Balakrishnan mentioned in her things are product related.

DR. BALAKRISHNAN: That's correct. So this is the summary of the SMQ analysis from the dulaglutide program. What the sponsor showed was actually the anaphylaxis SMQ and most of those events were urticaria. This came from table 56 in the background.

DR. CHEW: Would you like us, Dr. Smith, to answer the other questions or come back?

DR. SMITH: Yes. I assume there's no other

questions from the panel related to this point. Yes. Let's move on to the other questions.

DR. CHEW: We're going to do this quickly. Dr. Belder, the question on A1c by starting dose, pen A versus pen B?

DR. BELDER: Yes, Dr. Neaton's questions. Slide up, please.

The top line here in this graph shows the patients who had a starting dose below 30 and that would be the patients who were randomized to pen A or who were taking pen A due to their starting dose.

The second line is the patients who started at a higher dose, greater than 30 units, and they started on pen B. And their A1c reductions are displayed. We have a first plot of those changes. Again, the top two lines show the differences with overlapping confidence intervals.

I should note, however, that obviously, irrespective of which pen you were using, you were still titrating the insulin dose, et cetera. But it is as you said, the randomization is preserved

if you look at it this way.

DR. CHEW: Dr. Belder, stay up there. There's a question on the time course of 404 and 405 by FBG and not by just A1c.

DR. BELDER: Yes. So this slide was asked for. This is the fasting plasma glucose levels over time, starting from screening, then baseline towards the end of the study. This is study 405 where you see the little blip in fasting plasma glucose levels at week 4, indicating the insulin dose decrease.

Then the next slide shows for study 404 where you don't have that blip because all patients started at the same dose, at 10 units, and where essentially the Lantus and iGlarLixi curves are superimposable, indicating that lixisenatide does not contribute to the fasting plasma glucose levels.

I would like to note that we see similar efficacy results when we look at Lantus trials from other programs that we run. So these end-of-study fasting plasma glucose levels of around 117, 113

are what we see in our Lantus programs, even when there is a different titration algorithm or no dose cap. So this is the typical behavior of Lantus.

DR. CHEW: I think also there was a question of the addition of more aggressive targeting, more aggressive titration.

DR. EVERETT: So yesterday, there was some concern about this continued downward trend of the fasting plasma glucose towards the end of the trial. Here, it seems to be similar in the 2 treatment arms that we're really interested in, Lantus and iGlarLixi.

But how do you think that might have affected the hemoglobin, the achieved hemoglobin A1c, which was at 30 weeks when, even still at 24 weeks, you have a continued decline in the fasting plasma glucose in both arms of the trial? Is it a steady state, a stable glycemic state? And is the hemoglobin A1c accurately reflecting the glycemic state of the patients?

DR. BELDER: So, if we look at the insulin titration curves, that we see again that the

iGlarLixi arms and -- I want to see the insulin titration -- over time both arms are identical. And it gives you a little bit of a time course of whether or not stability has been reached.

If you look at these curves, it looks as if people are still increasing their dose over time. It's a little bit. It's not as steep as in the beginning. That might lead to further A1c improvements if the study would have been continued. But it would not necessarily have affected the treatment effect of iGlarLixi relative to Lantus.

The other thing is, now I want to see the other slide that you had up first. So we did look at the stabilization of insulin dose and those were curves that I think that you saw yesterday as well.

We see the stabilization of the iGlarLixi and Lantus arms here again in study 404. You see that there's absolutely no difference in reaching a stable level of insulin and the dotted line is where 50 percent of the patients reach a steady state or a steady level of insulin.

I hope that's it and, obviously, despite the fact that there's no difference in the insulin dose, we do see a better A1c, more patients at goal, and the mitigation of weight gain in this group.

DR. SEELY: In regard to that slide, was the Lantus-alone group held to a ceiling of 60 units?

DR. BELDER: Yes, that's correct. And I can show you there's not that many patients in this study who actually reached 60 units.

DR. SEELY: Yes.

DR. BELDER: I can show you that slide as well. So it was about 15 percent reached 60 units in study 404 relative to 94, a little bit more in the Lantus arm. Now, we can look at whether or not they reach their A1c goals, these patients, because obviously the ones that were at goal wouldn't necessarily need to go higher. And that is shown.

DR. SEELY: Right. But the concern would be the hemoglobin A1cs may appear similar because the Lantus group was capped and, if they had kept going up, they would have reached better hemoglobin A1cs.

DR. BELDER: And here, it shows that about 53 percent of the patients who were at the 60 units in study 404, in the iGlarLixi group, reached their A1c goal less than 7 and about 50 percent of the patients in the Lantus group. Now, obviously we have looked at other studies that we did with Lantus and see what can you expect if you titrate Lantus to higher. These patients, in both studies, who were at the 60 units had an insulin dose in units per kilograms of body weight around 0.6 units per kilogram. So that is in the range where ADA says, well maybe you may need to look at other therapies.

Having said that, there are some patients whose FPG level was not where you would like it to be. A lot of patients had FPG levels that were below 130. And some of the patients, as I just showed, actually have achieved an A1c below 7. Now we did, to assess the robustness of the efficacy, do tipping-point analysis. So we did it for both studies.

What we did there is for everyone,

irrespective of whether or not they reach goal. We started adding additional decrements of A1c to the last observed value. And then we calculated treatment effect and the significance level.

So if you do that for both studies, if you add about 0.2 or so additional point percent of A1c, if you add that to their reduction, then you don't see a difference in the treatment effect.

The statistical significance is only lost once you start adding about a full percentage point to these patients in additional A1c reduction. So we believe that the results are robust, that the capping obviously may have had an effect on the treatment effect, but wouldn't have affected the statistical significance.

DR. SMITH: Dr. Wilson, do you have a question on this same issue?

DR. WILSON: Yes. It's exactly related to this. Can you tell us about the experience in people for whom an endocrinologist would predict that they are going to need more than 60 units, which is complementary to what Dr. Seely is asking?

For instance, somebody over 250 pounds, I'm thinking this is not going to work for that person because they're going to quickly get to 60 or more units of the combination or glargine, et cetera. And just do you have experience with it?

DR. CHEW: I'm going to ask Dr. Meneghini to comment on that.

DR. MENEGHINI: So first of all, now, every patient reacts differently so it's difficult to predict. They also react differently if they're early on in the disease versus later on in the disease.

But you make a very valid point that, with the very overweight individuals, over 260, 280 pounds, getting to 0.5 units per kilogram per day may exceed those 60 units. So those are individuals that I may or may not try on this therapy depending on the conversation.

However, this therapy is indicated for the majority of people that we see who are not over 260 pounds to start with. If you look at the data that was shown, the average weight around there was

about 95 to 100 kilos. And in those patients, this type of approach with this cap should be able to get those patients to target and do so as you see with weight mitigation, low risk of hypoglycemia, and a low risk of GI side effects.

DR. SMITH: Yes?

DR. CHEW: There's a question about nausea and how it was evaluated. Could we have slide 87?

The nausea was evaluated as one would evaluate any clinical adverse event, was it clinically mild, moderate or severe. There was no special scale since it's kind of a symptom. And so you can see that, for the iGlarLixi versus Lantus and lixisenatide, it's less than lixisenatide, but as I was asked this morning, was reported more with Lantus.

So I think the follow-up question, what did that mean for patients who completed the trial successfully without discontinuing because of that? Dr. Belder?

DR. BELDER: So one of the analyses that we did to put everything kind of in perspective is to

look at what are the patients who can complete the study all the way to the end, reach an A1c level below 7, and were not discontinued either to nausea or were unable to titrate their medication and were not hindered by, for instance, hypoglycemia.

So these are the patients who successfully completed the trial. Everyone who discontinued was considered a treatment failure. And everyone who needed rescue therapy was considered a treatment failure. We see in both studies that the iGlarLixi arm are balancing things like nausea, et cetera, or perhaps events of hypoglycemia, and the iGlarLixi arm does better than each of its components.

DR. CHEW: There was also a comment made on the exenatide. Dr. Berria on the exenatide comparison?

DR. BERRIA: In the trial where we compared once-daily lixisenatide, I believe it was Dr. Yanovski that was asking the question. Versus twice daily exenatide, patients start out at baseline hemoglobin A1c of around 8 percent, after 24 weeks of treatment, experienced a drop in

hemoglobin A1c between 0.8 to 1 percent.

Now, we did in fact meet the criteria for non-inferiority because the upper limit of the 95 percent confidence interval was well below the prespecified margin of 0.4 percent. Most importantly, in terms of treatment success, in both groups, there was an equal percentage of patients reaching HbA1c target of less than 7 percent.

Now, it is also true that the lower limit of the 95 percent confidence interval was higher than zero, which would make the difference of 0.17 percent, statistically different. And these are the wonders of statistics. But at this point, I would like maybe Dr. Meneghini to opine on the clinical meaningfulness of such difference.

DR. SMITH: Do you feel you need that comment on clinical meaningfulness? Don't need the comment?

DR. CHEW: I'm sorry, Dr. Smith. I didn't hear you.

DR. SMITH: The question was whether the panel feels they need -- I mean, we got the numbers

and I don't know if the panel feel you need interpretation.

DR. SEELY: I have a question of how that fits with the FDA's slide 15 on page eight. I know you said something before, but it still doesn't make sense to me.

DR. CHONG: I'm sorry. Which slide again was that?

DR. SEELY: Your slide 15, page eight, where you give the mean difference versus exenatide BID 0.18, which to me looks like the exenatide is superior.

DR. GUETTIER: To you, it looks like lixisenatide is superior?

DR. SEELY: Under efficacy.

DR. GUETTIER: So I think you're referring to the study comparing lixisenatide to twice-a-day exenatide?

DR. SEELY: Slide 15.

DR. GUETTIER: So where the significance being --

DR. SEELY: It's the line where you have the

mean difference versus exenatide.

DR. GUETTIER: Right.

DR. SEELY: So with that 0.18 being positive, is that saying which drug is superior with that difference?

DR. GUETTIER: So the superior drug in this particular study is exenatide BID. The difference is 0.18 and you can see from the 95 percent confidence interval that the 95 percent confidence interval excludes zero, which means that the two drugs are different.

The primary objective of the study was a non-inferiority objective. So if they were below 0.4, they met the objective of the study. The non-inferiority margin is something that's selected before the study started.

DR. SEELY: Thank you.

DR. CHEW: Also, Dr. Seely asked about the comparison of lixisenatide and post-prandial glucose.

Could I have slide AA-9? Dr. Seely asked for the comparison of post-prandial glucose and its

related gastric emptying here. And what you see on the left is lixisenatide in blue, green as liraglutide.

What you see here is that the blue baseline is the peak, the hump, and then, after 8 weeks' sustained benefit, a flattening, whereas with liraglutide, both were gastric emptying and post-prandial glucose. Over the same time frame, there's less of an effect.

So the contribution of this to an outcome was also a question. And for lixi monotherapy, where there's no FPG component, it was superior versus placebo. So this does have a correlation with a clinically relevant outcome in A1c reduction.

Finally, just to wrap it up, Dr. Smith, could I have the risk management slide tying all of this together? We realize this is a novel combination. We feel we've characterized the safety and the benefits very well. But we will be proposing educational activities.

We're very experienced on the pens,

obviously. There will be information on the pen on the website not only for clinicians, but pharmacists and patients, with also live patient support program called Coach, as well as a customer service line. And we will have certified diabetes educators also working with these patients.

So it's a comprehensive approach for many of the issues that were discussed today. Thank you, Dr. Smith.

DR. SMITH: Thank you. So some people had questions. I had their names down for questions. It's been carried forward again. What we're looking for is requests for clarification. We're going to get into discussions. So Barbara Berney?

MS. BERNEY: Earlier, when we were talking about post-prandial glucose, it was suggested that this injection be given before breakfast. There are a lot of cultural differences and you said the largest meal. It has the most effect on breakfast, it has the largest effect. What happens if your largest meal is full of carbs at dinner? How do you dose that? How do you prescribe that?

DR. CHEW: You're asking about the full range of patients and various cultures. And Dr. Meneghini?

DR. MENEGHINI: That's a great question because not all patients eat breakfast. And so if you don't eat a -- and so it's indicated for breakfast or for the next meal of the day. Now, that is what the indication is going for.

As a clinician, as a patient, we can certainly discuss when is the largest meal or when are the greatest excursions in terms of post-prandial hyperglycemia. And we can certainly dose this before that meal. So as a clinician using this therapy, I see some flexibility in it. The sponsor, I think, is indicating it either for breakfast or the first meal of the day.

DR. CHEW: We have data on the effect given at different times of the day. Dr. Berria?

DR. BERRIA: Yours is a very relevant question. In fact, we thought about that and we did a study. And I'm going to show you the results. In this study we randomized patients into

a breakfast administration of lixisenatide once daily or their main meal of the day, whether that was breakfast, lunch, or dinner, the one with the largest post-prandial glucose excursion.

In fact, most of the patients picked lunch as their main meal. A smaller percentage picked dinner. Some of them picked, in fact, breakfast as the main meal of the day. Regardless, randomizing them into breakfast or their main meal of the day in terms of reduction in hemoglobin A1c made no difference. So they were non-inferior.

DR. SMITH: Thank you. Diana Hallare, did you have a question also, a clarifying question?

MS. HALLARE: I just wanted to comment on the diversity issue on studies 404 and 405. And they're on, I believe, the sponsor slides about 41-42 and 52-53.

I don't know if there's enough time to do a subgroup analysis on what for instance are the effects on -- I mean, with regards to what's the difference between Caucasian, black, and other race with regards to the effects on safety as well as on

the efficacy.

DR. CHEW: Yes. What we did here is by race. I'm sorry. This is the reduction between iGlarLixi and Lantus. And you can see that, overall, the treatment effect is preserved across several factors, including race, ethnicity, age, and gender.

I should say we did not get as many African-American patients as we would have liked. We need to do better there. We did go to sites where we thought we could have more patients recruited, black patients. We were not successful. But in future trials, we will certainly try to improve that.

With regard to safety, Dr. Sharma?

DR. SHARMA: When we looked at the safety profile across race, we really didn't see significant differences. The numbers are kind of small. One interesting point here actually when we look at the African-Americans is that we weren't seeing the levels of nausea that we were seeing in Caucasian populations. And I don't know how real

that really is, but overall, the events reported were pretty similar across race.

MS. HALLARE: Thank you.

DR. SMITH: So there are a few people who had their names down for questions and they may have been raised by others and things clarified. Dr. Burman, you still have a question?

DR. BURMAN: No, it was answered. Thank you.

DR. SMITH: Dr. Budnitz?

DR. BUDNITZ: Quick question on the selection of pen A or pen B in the iGlarLixi trials. I understand the insulin requirement, a selection criteria, but I thought in the FDA presentation there was some guidance based on GI symptoms. The pens might be switched from A to B or vice versa. Is that correct or am I misunderstanding that?

DR. CHEW: Dr. Belder?

DR. BALAKRISHNAN: In trial 12405, they were started on a dose that was half to two-thirds of their baseline dose. But if they were at a dose of

between 30 to 40 units, they were asked to take pen A as a preference. But if they developed GI intolerance, they switched to pen B.

DR. BUDNITZ: So my question is how often did that occur, and is that going to be part of the application that you switched the pen based on GI side effects.

DR. CHEW: I'm sorry. Could I have the question again?

DR. BUDNITZ: So the question is, is there a recommendation to choose your pen A or B based on tolerance of GI side effects for the lixi component? And is that part of the application?

DR. CHEW: No, the submission is the patients who are de novo will start at the low dose of pen A, each pen, at 10 units and titrate up within that pen. And they would titrate up within that pen. And if required, they could go down on that pen. But that would be up to the physician. We wouldn't be mandating that. You titrate up according to your insulin needs, and you can adjust by titrating down on the yellow pen and that would

be the preferred way.

Let me say right now, what is the titration? The titration for the de novo patients is to go from 10 all the way up to 40 if they need to, on the yellow pen. That's the top of the pen. Then if they need to go up, they will go up to 40 and continue.

DR. BUDNITZ: Again, that's a little bit different than what I'm hearing from FDA. FDA is saying that they have a choice when you're between 30 and 40 units of which pen you want to use.

DR. CHONG: So I think some of the confusion may have to do with what was the protocol design in terms of how they would manage that transition range and what is the proposed indication for when you get in that transition range. What the sponsor is submitting in their proposal is that if you start on pen A, you go all the way up to 40. If you need more than 40, you switch. There's no specific language or proposal to say if you are between 30 and 40 and you have intolerable nausea, vomiting, you would switch. That's not what

they're proposing.

DR. CHEW: We are not proposing that. That would lead to confusion. You titrate up all the way on the yellow pen. If you need to, you switch and you stay on the green pen if you need to.

DR. SMITH: Dr. Wilson, on the same point?

DR. WILSON: It's similar. It's analogous. If you titrate down, is there a possibility that you're going to stop the combination and you're going to go simply to glargine?

DR. CHEW: If patients cannot tolerate the green pen or the yellow pen, they should stop the product.

DR. WILSON: Now, my question is, if you're down to 10 units of glargine plus the combination, you're at such a low dose of the second drug that perhaps it's not needed. That's the question. If you started with a combination product and you've never had glargine, it may be that you're at an A1c of 7 and you're doing great and maybe you don't need a combination.

DR. SMITH: Dr. Skolnik, this would be the

patient who is needing very little of glargine or iGlarLixi that were on the 10-unit starting dose.

DR. SKOLNIK: Sure. And I think your point is a good one. You never know ahead of time. You only know in retrospect where your A1c is going to end up. So in the appropriate patient, we would start iGlarLixi at 10. We might titrate up in some people a lot, but your point is well taken, in some people not very much.

My understanding, though, from the data is that we're still getting a better A1c result in the people who are even on a low dose compared to a similar dose of Lantus. Could you decide to switch just to Lantus? Of course you could and I think that's going to be again that discussion with the patient.

Of course, the downside of doing that would be the type of scenario that we talked about with the patient I presented, Betty, where her control on her basal insulin is there for a few years, but then it goes out of control and we risk what is so common, which is therapeutic inertia.

I think we heard about it in the public forum, the dislike of adding a second shot. So that's going to be a discussion again, between patient and physician to come up with the right choice.

DR. SMITH: Dr. Nason, do you have another question?

DR. NASON: Thanks. I just had wanted to go back to the slide that I'd originally asked for, which was 28, if that was possible. It was the one just about injection-site reactions, and that was one where I just had wanted to clarify just the timing of both the antibody measurement and the injection site reaction or hypoglycemic condition, I should say. Either one of those was on that slide.

Just to make sure, was it, as you guys said, the highest possible antibody versus did they ever have any sort of reaction? I was just trying to understand the timing of that.

DR. CHEW: If I can understand, the question is, it's which ADA was chosen and how the analysis

was done? Is that for FDA or for us?

DR. NASON: Yes, so for this, everybody sort of tallied up as to whether they were ADA positive or negative, and then at the bottom what the level was, if it was measured, and then whether they had any hypoglycemia, and whether they had an injection-site reaction.

I just was trying to understand whether this was again a maximum of an antibody and an anytime reaction. Or were these two linked in time in any way? Was this an antibody at the visit before the reaction or something like that?

DR. CHEW: The timing of the ADA relative to the event I guess is the question. Dr. Sharma?

DR. SHARMA: The answer is no, they wouldn't be necessarily linked. When we did these analyses, again, if you were ADA positive at any time, you were counted as positive. The injection-site reactions tended to be early in the course of the event, so there's a possibility that the event occurred without the presence of ADA.

DR. NASON: Okay. And the level there at

the bottom is again the maximum?

DR. SHARMA: Yes, it is.

DR. NASON: Okay.

DR. GUETTIER: The other thing to just remember is that antibodies change over time. And the specific serum type of antibody will change over time. So this, I think -- and I'm going to call on my immunogenicity colleague perhaps -- is an IgG antibody that is being tested and so we wouldn't necessarily catch IgM, IgE with this particular assay.

DR. DICKENSHEETS: Thank you. I'm Harold Dickensheets. I'm the immunogenicity consult team leader. And to address Marc's point, the assay, in my understanding -- and the sponsor can provide more detail if applicable -- would only capture IgG. So the other subclasses would not be necessarily captured.

DR. CHEW: That's correct.

DR. SMITH: Okay. Dr. Yanovski?

DR. YANOVSKI: Sure. Can we look at the FDA's slide on the safety, slide number 11 on

hypoglycemia? Are you going to pull that up? Or I could just ask, which is I just wanted to clarify, I wanted to make sure, it looks to me as though there is no difference between the levels of documented hypoglycemia between the insulin glargine and the iGlarLixi groups. Is that correct?

DR. BALAKRISHNAN: That's correct.

DR. YANOVSKI: So in this case, there's no kind of decreased hypoglycemia with the combination?

DR. BALAKRISHNAN: No.

DR. YANOVSKI: Thank you. I just wanted to clarify that.

DR. CHEW: I should comment that there has been no combination that has shown a benefit of hypoglycemia using the ADA criteria.

DR. SMITH: Dr. Meisel?

DR. MEISEL: But it is true that, if you take a subgroup of people with severe symptomatic hypoglycemia, that was actually higher with the iGlarLixi group. Correct?

DR. BALAKRISHNAN: In the second study, in the study on patients who were on prior basal insulin, the EFC12405, there was no severe hypoglycemia in the iGlarLixi group. There were about 4 patients with 5 events versus 1 in the insulin glargine arm.

DR. CHEW: In those cases, Dr. Sharma, could you explain those cases, the imbalance?

DR. SHARMA: Certainly, we did see that difference of 4 and 1 and we felt these were really low numbers that we were trying to compare because the overall rate of severe hypoglycemia was really very low.

Questions to Committee and Discussion

DR. SMITH: If there aren't more questions from the panel, I would propose we move to the questions to the committee. And I'm not seeing hands and questions.

So we'll proceed with the questions to the committee and the panel discussions associated with those questions. I'd like to remind public observers that, while this meeting is open for

public observation, public attendees may not participate except at the request of the panel.

So if we could bring up the first question, we'll try to keep our discussions, as much as we can, focused on the specific question and try to move expeditiously. We've got five of these we want to deal with. And there is some overlap sometimes, so let's try to be focused. I'll read question, discussion question 1, or discussion point 1.

Discuss any issues related to the efficacy or safety of lixisenatide for the treatment of patients with type 2 diabetes mellitus.

Please comment on whether any of these issues preclude approval of lixisenatide. So this is not focusing on a combination. This is focusing on the drug lixisenatide and the data we've heard on that. Would anyone like to make any comment on this discussion point? Dr. Budnitz?

DR. BUDNITZ: So I want to make sure I understand. So the indication is going to be requested in combination with a sulfonylurea. If

that's correct, then I think one concern is hypoglycemia.

It looks like that there is maybe a fivefold rate increase in hypoglycemia, looking at sponsor slide CO-67. And so I think that is just something to note. I don't think it precludes necessarily approval, but just a concern to make note of that combination, risk of hypoglycemia.

DR. SMITH: So I'll also make a comment, which is that, in reviewing, this represents a drug which I point out would be the sixth member of a similar drug class. In the efficacy data that we've seen, my interpretation is that it has efficacy and that it is in general comparable to other drugs within this class.

In terms of the safety data, I have not seen concerning safety data for the most part. The cardiovascular data are quite reassuring from the rather large ELIXA study. The one point that I think is worthy of note that we've discussed to some extent is the concern about severe allergic reactions, and, A, the possibility that they may

occur in patients, and, B, the perhaps not-fully-resolved possibility that there may be a greater occurrence with this drug than from some other members of the class. And I don't think we can conclusively know that.

We have not seen evidence that these can be predicted. That's perhaps not surprising, but we press that point anyways to not miss something. But it appears that they can't be predicted by what we recognize now from pre-treatment characteristics of patients.

Although 60 percent of them occur within the first roughly two months, there's a continued occurrence of severe reactions. So putting an initial window of intense screening, to my impression, my feeling, isn't really workable. It wouldn't protect against a large enough percentage of the reactions.

So that my sense from a -- none of these issues to me would preclude approval of lixisenatide. They would, perhaps one might say, support approval, although, specifically, caution

in terms of ongoing monitoring of this drug is approved regarding severe allergic reactions, I think, would be something that should be given serious consideration.

I would also note that, overall, the safety database is still pretty small. The number I recall from a series of pooled studies was 995. And so I think, again, there should be recognition that, whereas there's reassurance from the experience with other drugs in the same class, with this drug itself we still have a limited safety database. And so ongoing monitoring would of course be something that would be important to consider.

If people would like to add to that or disagree. And Dr. Seely had a comment here.

DR. SEELY: So I agree with Dr. Smith in terms of at least the drug shows efficacy in terms of non-inferiority to another drug of the class. The diligence of the company, who actually carried out the cardiovascular safety studies I think, even though it was an FDA maybe request, still deserves

to be applauded.

One of my questions about whether the allergic reactions actually are increased with this drug over others is that I think the company had in place a very, very sensitive detection system for picking up allergic reactions that may not have been as extensive for the previous drugs in this class, some of which we found out had a lot of the allergic side effects in post-marketing studies. So I don't know that this slants us to that there's more.

I think probably the statement should be that, in all drugs of this class, we need to be vigilant for allergic reactions. And the only thing we can really compare well is the post-marketing studies of the other drugs and, if this drug gets to market, the post-marketing studies that would occur on this drug.

DR. SMITH: I would agree. And Barbara Berney, did you have some comments to make?

MS. BERNEY: I'm not a medical person, so I don't know whether this has relevance or not. But

there are patients -- I'm one of them -- who have allergic reactions to a very wide range of medications. In fact, Actos, I had a terrible reaction to within an hour of ingesting it.

If a patient has -- and it's a long, a wide range of medications, not just diabetic medications. If a patient has a history of weird allergic reactions, would that be a predictor of the possibility of an allergic reaction to something like this? I mean, if my doctor suggested to me, you want to try this, I would say no because I already know that, too many times, I pass out and hit my head on the floor.

DR. SMITH: Well, you've directed that system within six questions to me and I would prefer not to answer.

(Laughter.)

At least, you're looking at me. I would prefer not to answer that question in this context right now.

If you were my patient, I would take a detailed history. I would explore the specific

agents to which you had reactions and the nature of those reactions.

Then I would work with you to make a decision that was a combination of what you were comfortable with and what I felt was medically appropriate. But I think we shouldn't explore that. I would propose we not explore that at extent right now because I think it's not quite enough at this --

MS. BERNEY: I wasn't talking about myself specifically, but in general.

DR. SMITH: Right. But that answer, I would apply across the board. Other comments to add to this discussion?

DR. NEATON: Maybe I heard you wrong, Dr. Smith, but that would be my major concern as well, the allergic reactions. But the database they have is over 7,000 people and so I thought actually 4 events that were really severe is what I'm understanding. And the others were grade 1, grade 2, which probably did require much more careful surveillance. Was somewhat reassuring that it's

not a large percentage of people that are going to be exposed to this potential risk.

DR. SMITH: Yes. Actually, I know the number I quoted, which I pulled off a slide, but knowing about the ELIXA study, actually, your number makes sense. But it doesn't change the ultimate statement about how one would wish to follow up. Dr. Nason?

DR. NASON: So I'm not sure. The one thing I just want to throw back into the mix is, I don't really know how to think about the antibody data, too. It seems like a high ratio or a high rate to me to have 70 percent of the people with an ADA by 70 percent. This is not my field, though, so I don't know that other drugs wouldn't have that as well.

I was a bit unsatisfied, I think, with some of the slides and some of the exploration about either anaphylaxis or reactogenicity, how that might have correlated with the antibody data in time, too. So I don't know whether that antibody data is part of this same discussion about

anaphylaxis or allergic reaction, but I'm still a little unsettled on that issue.

DR. SMITH: From your perspective, would that preclude approval of the drug? That's the discussion question.

DR. NASON: I'd love to ask that of my clinical colleagues and see what they thought the relevance was of that ADA in such a high rate by 70, because I don't know.

DR. SMITH: No, that's fair enough. I got you. Are there other comments on this before we move to the next one? Yes, Dr. Meisel?

DR. MEISEL: After everything that's been said, I still have lingering concerns about the allergic reactions. An additional concern that I have is whether this is really a BID drug that's being pasted up to be a once-a-day drug.

I mean, according to the FDA slides, the half-life of this drug is an hour and a half, which means that it's going to be functionally out of the hours or so. And we've seen data that shows that, by suppertime, the effect is half at best than it

is at breakfast time, assuming you take it in the morning.

If you take it with the big meal of the day, maybe do it at supper, then probably nothing is left by the time breakfast comes along. And all of the data that is present shows a small but statistical improvement in all parameters once given BID. And so my concern is whether or not a once-daily dose is the right dose or whether it should be both doses that would get approved.

Then that brings another concern that, if it's only once a day, the clinicians recognize the problem. Will they end up prescribing it twice a day anyway? And then what implications would that have, particularly when we start talking about the combination?

DR. SMITH: Any other comments on this point?

(No response.)

So to quickly summarize, it sounds like, as a general consensus, the panel does not see issues that would preclude approval of the drug. And

that's from a perspective of recognizing there is efficacy that appears in the ballpark of other agents in this class, and adequate efficacy, and that there are not safety concerns that would preclude it.

There have been, for multiple panel members, concerns expressed about the allergic reaction potential and uncertainty about the magnitude of that, whether it's different or not different from other drugs in the class being not clear. And so having said that in general has not been seen as something that would preclude approval, the recommendation from the panel members, for the most part, would be one of monitoring.

There was concern raised about the possibility that lixisenatide might actually be more effective if used twice daily based on efforts to interpret some of the pharmacokinetics and some of the other data.

That leads to another concern, which is that, if this drug were approved, would physicians or patients perhaps recognize that and utilize it

in a way that may not be what is recommended, that is, tend to use it or at least under some circumstance use it twice daily? So it's just something I think for the FDA to think about and talk about as this goes further forward.

So I would propose that we, if you don't have additions or subtractions, panel members, yes, I've got some questions here. Dr. Parks, did I see your hand? I did not. Dr. Neaton?

DR. NEATON: I just think Dr. Nason raised a good point. Quite frankly, it's hard for me to comment on it because I don't think either analyses that were done make a lot of sense. But I think understanding by the sponsor and the FDA this antibody data and how it potentially might impact efficacy and safety is important to do. That may require additional studies.

But I guess the other question in my mind was, is if antibodies developed to this drug and if it impacts efficacy, would it basically impact other drugs in the class? And so I think it's important to sort it out. And so I don't think we

should leave that one hanging, I guess is all I'm saying.

DR. SMITH: Dr. Wilson?

DR. WILSON: Yes, perhaps we could hear from the FDA's immuno expert. And the point is that for clinicians, we're used to seeing antibodies against non-human insulin, for instance. I would expect antibodies against large peptides to occur. And it's not a barrier to care at all. And it's IgG related. The acute reactions we're especially concerned about are probably IgE related.

So the clinicians are used to seeing antibodies against it. But perhaps an expert could weigh in on that and assuage our concerns about IgG-related antibodies in proteins and peptides.

DR. DICKENSHEETS: So that is one of our lingering issues that we are concerned about, the potential cross reactivity of anti-lixisenatide antibodies with either endogenous GLP or other GLP analogues. But that is a review issue at this point. We don't have any further data to discuss regarding those issues.

DR. SMITH: So as a clinician and not an antibody specialist, but with experience with insulin antibodies, for example, and their potential impact, it actually is very complicated and it can be drug specific or agent specific. And it can be the type of antibody specific, so one can have sequestration of an agent that actually prolongs its active effects.

One can have a simple blocking of an effect. One can have release of larger quantities, which has been well described with insulin. And so actually, empirical data are ultimately what I think is needed in this realm of circulating antibodies and trying to translate that into some vision of action.

That kind of underlies my position of feeling that monitoring is what's needed. In other words, data are needed. It's not possible to very precisely predict the implications of something like elevated antibodies.

If we can move to discussion question 2, this topic is, discuss the benefits of starting a

fixed-combination drug product containing lixisenatide and insulin glargine in patients with type 2 diabetes mellitus not treated with either a basal insulin or a GLP-1 agonist, i.e. starting two new drugs at once.

In your discussion, identify the patient population in whom this use would be particularly useful and address why you would select the fixed combination over use of an available GLP-1 agonist or basal insulin in these patients. Explain your rationale using data from the briefing materials, presentations, or your own clinical experience.

So what we're talking about here, specifically, are patients who are naïve or at least at this point are not at the point of initiation, are not taking insulin or a GLP-1 agonist. They may be taking other drugs.

The question has to do with starting this combination, which would start two agents at once, or alternatives that one might consider of starting just insulin or just GLP-1. And I'm going to get to you, Dr. Burman. And it's also asking for some

comment or thought about specifically which patients one might use this combination in. Dr. Burman?

DR. BURMAN: Thank you, Dr. Smith. I think this is really one of the seminal questions and I have a difficult time coming to an answer. But the question doesn't take into account A1c or control.

So if you're discussing starting someone who is naïve to insulin or anti-diabetic drugs with a hemoglobin A1c of 7 to 8.5 or 9, if you start this combination, you would probably be starting something, an agent that they may not need because you don't really know that they need two agents. So you're spending time and money, and exposing someone to the possible side effects of two agents when they really needed one.

On the other hand, if you take what Dr. Ratner said, their recommendation from the ADA that someone should have poor control with a hemoglobin A1c greater than 9 percent, random glucose greater than 300 -- I'm sorry, A1c greater than 10 percent, a random sugar greater than 300.

I think that's right. Then if you're starting two agents, you're not going to be able to reach a high enough level in many patients.

There are no studies comparing the combination agent to what would be the standard now, which would be long-acting insulin plus short-acting insulin before meals. I realize there are advantages to 1 injection a day versus 4 and other issues to bring up.

But I think, given those issues and the possibility of someone having resistance, if they're obese, et cetera, I can't decide in my mind which patients I would start who are naïve to insulin or anti-diabetic therapy on this combination.

DR. SMITH: Other comments? Dr. Seely?

DR. SEELY: I think I represent the more of a purist point of view. So I'm concerned, in general, about starting two drugs at the same time for several reasons. One is I'm not sure the second one is going to ever be needed or will be needed in the next several years.

The second is, there's usually a substantial increase in cost in a combination drug compared to a single drug.

Third and really important is that there's a lot of side effects to drugs that are often placebo side effects that, as clinicians, we really struggle with figuring out which drug a person's reacting to. So if I have someone with hypertension and diabetes, I often won't start the anti-hypertensive on the same day I'm starting the drug for the diabetes.

So I would go more to that this would not be my first line of drug on someone who had not been on either agent alone and that I would pick a single agent. And we'll get into number 3, but number 3 is a scenario where I see this being useful.

DR. SMITH: Dr. Wilson, you had your hand up.

DR. WILSON: I think I'm in the group with one at a time. Most of us treat metabolic conditions with one at a time. I could see there

may be some opportunities.

One of them is for whom I echo Dr. Burman's -- this is for the person who is 8 to 10 who can't handle the usual regimens that we have laid out by ADA guidance and maybe a person with metformin intolerance because that's our cornerstone first drug, but in general, it's one at a time, I think.

DR. SEELY: In terms of reality, sitting there thinking in my office, what I imagine is, by the time I get the prior approval for the combination, I need to start something. So in reality, I probably am going to start a single agent because the prior approval will take me days.

DR. SMITH: Dr. Everett?

DR. EVERETT: This is a question for some of my colleagues on the panel here. If you have a hypothetical patient with an A1c of 8 to 10 and you were considering starting insulin for that patient, would you think about the dual therapy because of the differences in the weight gain that we've seen with this agent and with others in a similar class?

DR. SMITH: So I'll respond to that. And I'll sort of respond a little more favorably than I'm hearing from some of my colleagues here. I share all the concerns and I practice the same way, which is that I have concern about the side effects of one drug when I start that drug. And that is multiplied when one starts two. So I feel a resistance to starting two different agents simultaneously.

Nevertheless, there is a group of patients for whom the issue of weight may be very significant. There are patients who are insulin naïve who arrive with an unwillingness to take insulin. There's a host of concerns that they might express that may not be data supported, but they express a data-supported concern about weight gain.

So I think, at the level of combining the physician's judgment in terms of risks and benefits against the patient's wishes or potentially the patient's willingness to take a drug at all, depending on what they see as problematic side

effects such as weight gain, I think there's a group of patients where I would envision I -- it may be a small group -- may end up using this drug.

That could be someone who's previously been on insulin and had a bad experience in terms of, weight gain -- that's what I'm thinking of -- or someone who simply believes that from what they have learned from reading, or physicians, or friends and other non-professionals.

So I think that's a category where, then, the risks that I may be counterbalancing would be the risk of two drugs versus the risk of not initiating a treatment that's potentially adequate for an unacceptable degree of glycemia. So that's a group where I would see that.

Yes, Dr. Seely?

DR. SEELY: I just have a comment back to that. I think part of my feeling about that depends on whether we feel comfortable using a secondary outcome of a study to say we believe that this combination actually limits weight loss that we see with insulin. And remembering that it was a

secondary outcome, so it wasn't designed to look at that one, are we convinced that the data shows that it prevents insulin-induced weight gain?

You can say to a patient, "This drug is purported to," and the patient is going to be happy to try it. But I think, how much confidence do we all have -- and I'm interested in other people's opinion -- that, by using the combination, we can actually prevent insulin-induced weight gain?

DR. SMITH: Yes?

DR. KEWALRAMANI: I wanted to not comment as a clinician, but rather go back to some of the data that we have here. The points around the patients that you made, Dr. Smith, I think are important, but I also look at study 404 here, which is indeed a study of patients who are the patients in this question, which is to say patients who are neither on GLP-1 or insulin.

The data that were presented do show a good response in terms of hemoglobin A1c. And if I look at the inclusion/exclusion criteria again as a starting point, there are criteria around A1c of

7.5 to 9.5 or 10 or A1cs of 7 to 9 that can start to develop a population that could benefit from this drug as a drug for those who are naïve to GLP-1 or insulin.

DR. SMITH: Yes, and I will respond to Dr. Seely. And I think we could use more data, but I think the data were internally consistent to the extent to the data we have. And given data available with other drugs in class, I would have a fair amount of confidence not feeling that this had been perhaps adequately established. I have a fair amount of confidence that there really is a weight effect of the drug.

I think that even modest amounts of either weight reduction or prevention of modest amounts of weight gain can be very significant for patients. And so 2 kilos as a percentage body weight is not very much, but 2 kilos can mean a lot in terms of how patients feel about the medication, and their state, and also perhaps even their willingness to take it or continue it. Again, I can't quantify that. But I think the weight effect is probably

modest and real. And that's extrapolating from what we have in the data. Dr. Yanovski?

DR. YANOVSKI: Yes, I think I mentioned this before, but not today, which is that one way to look at this is to actually look at weight change categorically. Those who have gained 5 percent or more of their body weight with either this drug or with insulin, and look and see if there's a difference. And the sponsor may actually have those data. If not, they'd be easy to get.

But one thing I think we -- I don't know how many of the patients in these studies, I think the mean BMI was just about 30. But I don't know what percent of patients had a BMI of 35 or more, class 2 or class 3 obesity, but it's certainly a high percentage of the diabetic population. It's more than 15 percent of just the U.S. adult population.

So there have not been studies that have really been looking at this heavier group who are likely to be more insulin resistant and a group that's more likely to need more than that 60 units

of insulin. I think that that should be studied.

DR. SMITH: More comments or should I try to summarize?

DR. MEISEL: One brief comment, and that is when we start a new drug like this, the value would be is if we could use lower doses of both. Right? We see that in hypertension nowadays, where you start with the lower doses of two drugs as opposed to maxing one or the other.

But in this particular case, this combination is not insulin sparing. We end up with the same dose of insulin regardless in all the groups. So the advantage that could exist with a fixed dose starting as a fixed dose doesn't exist in this case because it's not insulin sparing. And I think we need to keep that in mind.

DR. SEELY: So I was interested in people's opinion about this scenario. To me, having everything in one injection is really appealing in terms of patient acceptance. So if you're going to give a once-a-day insulin with this lixisenatide, would an alternative be giving a once-a-week GLP

agonist with daily glargine?

Now, it is true that 1 day a week you give yourself two injections, but 6 days a week, you're still just giving yourself one injection. So I was wondering people's reaction to that, because I thought of that as an alternative.

DR. WILSON: Can we come back to that with number 3, discussion item 3, what she just raised?

DR. SEELY: It applies to this one, too.

DR. SMITH: Because it would be an alternative way of starting 2, yes.

DR. SEELY: Yes, as long as we discuss it, it doesn't matter.

DR. SMITH: Let's make sure we do because I also have a comment on that. So we can come back to it later.

DR. WILSON: There's some appeal to that. I don't think many of us have that much experience with the once-a-week injections of exenatide. There's only one product right now that does that. But it's appealing. I'm not sure there's that much data with exactly what you're proposing, though.

DR. SMITH: Let's discuss it a little bit. Any other comments on this point so we don't leave it hanging? I have a comment, again, from clinical practice, which is, when I do the math, that makes good sense. That's 8 weekly injections instead of 14 and it's eight versus seven. So it's close to seven.

My experience with medications is that those that are taken at a somewhat irregular schedule, such as once weekly, actually can be difficult for patients to remember and to reliably take their medication. And it takes more regimentation than even for the daily med. And a daily once-a-day med takes regimentation.

So it's not as simple as the injections. I don't think we have the answer to this, but if one weighs those, it's an option to consider. It would be an option that users could consider. But it's not so simple as the math in order to make it work, in my opinion from experience with practice.

DR. SEELY: So I would disagree. My patients are doing really well on once-a-week

anti-absorptives for their osteoporosis.

DR. SMITH: Yes, Dr. Chong, you wanted to make a comment from the FDA on this?

DR. CHONG: Yes, I just had one more comment. Dr. Wilson mentioned there's only one. There's actually three weekly injectable GLP-1 agonists.

DR. SMITH: So should I try to just summarize and then we can go to the next question or you can correct my summary? Dr. Neaton, I think I left you out of a comment. Did I?

DR. NEATON: You covered my comment. But actually, I was going to just maybe chime in on what Dr. Meisel said because it does seem pretty clear. You're talking about a situation where you're going to start insulin and consider whether you want to use a combination. And, you know, the other possibility I guess would be not starting. Consideration might be kind of borderline with insulin, start the GLP.

But it does seem like in these studies, as well as what we saw yesterday, possibly because of

the dose, that the GI side effects are less with the combination than with lixi alone. And that would seem like a plus. And maybe more generally, you know if one was used to using this, the notion of using lower doses potentially of two products is an attractive thing in my mind.

DR. SMITH: Yes, and I guess I might respond to that, that I agree with that. And I guess particularly if you're -- it's tricky because you're introducing it at a lower dose, where perhaps you're getting less side effects, but you're also using it at a lower dose.

So it gets almost back to a comment that Dr. Reed made at one point, which is the difference between considering this as two drugs and as one drug that happens to have two things in it as you try to think your way through how it works.

So I'll try to summarize and we can amend what I say. But in general, it's been difficult for members of this group to define or identify a population of patients where they feel they would be comfortable starting the two agents at once, or

at least a large group of patients because of concerns about the risks of starting two agents at once and the potential for efficacy with using the individual components in a sequential manner rather than a simultaneous manner. And this is in this context of somebody, a patient who is not on either drug.

An argument's been made that, for some patients who the consideration that this may have a favorable effect on weight gain with insulin, that may be an important motivator for them that would encourage or convince them to use the drug in this combination.

It's been noted that there might be some alternatives to using the two agents, but not in a combination such as this one with something like a once-a-week GLP-1. That's not what we're here to judge, but the point has been made that there may be alternatives there that might in a sense compete for the population that would ultimately use this drug.

The point importantly was made that, being

that this combination drug actually brings a lower dose of GLP-1 receptor activating drug at the same time that it's being started together with insulin, that actually may be responsible for lower side effects and may somewhat diminish the concerns about the side effects in starting two agents at once.

So if we view it as a drug rather than two drugs, that the pooled risk of those may actually be less than one tends to think when you think about the individual risks for those.

Would anybody like to add to that slightly jumbled summary I provided? Dr. Reed?

DR. REED: The only thing I would add to that is, looking at the primary endpoint of A1c, it still had the best effect relative to either one of the agents used alone. Now, I don't think we can explain why relative to dose response, but the fact is the fact. It's more efficacious as well.

DR. SMITH: But I don't think we fully resolved the question of whether insulin was used optimally in terms of that comparison. So you're

correct in the data that we looked at, but I think there's some debate about how exactly to interpret those data. And if insulin was used according to protocol and some of the protocol has limitations, perhaps one would have seen more efficacy from the insulin-alone arm in those studies. Dr. Nason?

DR. NASON: So I just want to play devil's advocate a tiny bit or maybe glass is half full, glass is half empty. I'm thinking back on that slide where they looked at the early nausea, and vomiting, and diarrhea, and headaches in the early phase of the first 42 days, I guess. And the combination really does have more nausea than insulin alone. It does certainly have less than lixisenatide alone, but it does have more than insulin.

So I just want to sort of throw the counterpoint that you raised where you wanted to have someone try insulin who is afraid of the weight gain. And I just want to make sure that we're also aware of the possibility you could have someone try the combination and stop taking it

because of the nausea, whereas they would have been fine on insulin.

So it does have a lower nausea profile, certainly, than the lixi alone, but it's still double what the insulin was and that will mean that some people will have a negative experience with it. That's all.

DR. SMITH: Move to the next discussion topic. So discussion topic 3, discuss the benefits of using the fixed-combination drug product containing lixisenatide and insulin glargine in patients with type 2 diabetes previously treated with either a basal insulin or a GLP-1 agonist, i.e. adding a single new drug by using this combination to an existing regimen.

In your answer, identify the patient population in whom the use of the fixed-combination drug product in this manner would be particularly useful. Explain your rationale using data from briefing materials, presentations, or your own clinical experience. So, Dr. Burman?

DR. BURMAN: Thank you. I think this might

be a circumstance where the combination drug would be useful and I won't reiterate the ADA guidelines, but that seems to be a reasonable starting point.

But I would raise the issue that you're including in this discussion adding it on or substituting, if you will, for a GLP-1 agonist where there are no studies on that. And I don't know how appropriate it is to approve a drug when there are no studies showing that it works in that individual circumstance, although theoretically we think it might.

DR. SMITH: Dr. Wilson?

DR. WILSON: So I think this is probably the time and place where this product would be used. So the type of patient I can imagine would be somebody who has been on a metformin, perhaps, most commonly plus a GLP-1 agonist, so now on two drugs.

You've already got one injection going and the person's not at goal, probably close to 8 to 9 plus. And this medication is going to bring them down another point, get them close to 7, which is going to be the goal for most patients.

Especially helpful would be the person who's obese and is concerned that he's obese or she's obese, the person whose weight is under 250 pounds probably, because if he's really heavy, this might not be the right thing for him. And that A1c that I was saying, that window of opportunity, I would say, is where I would think to use it.

DR. SMITH: Dr. Seely?

DR. SEELY: So apart from the labeling issue and the pen, which I know we're going to discuss next, to me is the ideal situation to use a combination drug, that someone's on a single agent in your combination drug and you want to add the second agent in your combination drug. And you can do it in one delivery. So to me, this would be an ideal situation for the combination if we could solve some of the issues in discussion 4.

DR. SMITH: Thanks. And Dr. Everett?

DR. EVERETT: I think this again is the right context. I share Dr. Burman's concern about the lack of data for adding this drug to a patient's regimen who is on an established GLP-1

agonist. I suspect it would work, but there are no data in the development program to suggest that that transition would go relatively smoothly.

There are of course data in the 405 study for the basal insulin transition. And actually, to that point, some foreshadowing. I think the two fixed-dose delivery systems are actually ingenious in that regard because it allows you to add a single injection for two agents to somebody who may have been on a more substantial dose of insulin as their baseline regimen.

DR. SMITH: So I'm going to summarize and maybe add something and then we'll see what else you'd like to add. So this notion of a patient group where one of the two components of the combination, the patient is already taking is viewed much more favorably as a candidate patient group for use of the combination agent.

It is noted, however in that context, that there actually are not formal study data on one component of what's in this discussion question, and that is subject patients who are already on a

GLP-1 agonist. And we don't actually, for this specific agent, have those data. We have it for somebody who's already on basal insulin.

So I haven't heard great concern expressed because of that circumstance, but it certainly is worthy of note that there's a lack of data in that regard. The sponsor did mention that they're considering and apparently going to undertake a study to address that issue. So the FDA could grapple with the question, I think, or my panelists can comment on whether that should be a pre-approval or a post-approval context for that study.

There was concern expressed that, within this seemingly best target group, there are actually limitations on what we know about subgroups of patients who might fit this group. And one example mentioned was patients who may have very marked obesity, presumably with a very marked insulin resistance. And we just have a lack of data, I think, to probe how broadly this would apply across the whole spectrum of seeming candidate patients.

What I haven't heard people express concern about is the starting dose of the GLP-1, whether in the context of our last discussion or this one being one that's less than what's approved as a therapeutic range.

So I'll just make my own comment that, from the limited data that I have seen with the lower doses of the GLP-1 analogue, again, I think there's a pretty strong argument that it probably has some effects, although they may not be maximal therapeutic effects at a lower dose.

We do have data about what results from use of the combination, so that doesn't give me much hesitancy, the notion of using a lower dose because -- and this was discussed a little previously -- I also know that the lower dose appears to also be associated with lower side effects.

So in a sense, the compromise in efficacy is offset by a reduction in concern about some of those side-effect risks. And in the end, we have the efficacy data that emerged with the

combination.

That's my summary. In addition, if anyone wants to add to that, Dr. Neaton?

DR. NEATON: I just was going to add, I mean, it clearly it looked like, just looking at study 005 [sic], the combination, one, on hemoglobin A1c, there was not an effect that was obvious on hypoglycemia. So that was kind of mentioned before more generally.

So you're kind of giving up -- you're going to have a somewhat higher incidence of GI side effects and what you're going to gain in terms of other potential side effects with the combination is less weight gain. And so it's kind of that balance.

It seems like it's pretty clear from the data that you get modest -- but all this is over just 20 or 30 weeks, so it's a relatively short-term set of data that you're working with when these drugs are going to be used for a much longer period of time. But it seems like that's where the balance has to come in, in terms of

making a judgment.

DR. SMITH: And it's also one injection instead of two if you're comparing it to the use of both administered independently. Any other discussion on this point? We can move to discussion point 4. And this is a bigger one and I propose we take this in two parts.

So to start reading it, discuss clinical concerns related to the use of the fixed-combination product which combines a drug that, when used alone, has a wide effective dose range and is titrated to effect on a continuous scale, i.e. insulin glargine, with a drug that, when used alone, has one or two recommended effective doses, i.e. lixisenatide.

Specifically discuss, and let's just take the first of these right now. Specifically discuss issues related to loss of dosing flexibility, including but not limited to use of potentially ineffective doses of one agent in populations with low insulin requirements, inability to dose the two drugs independently with the device presentation

proposed, inability to increase the insulin dose beyond 60 units.

We'll get to presentation of device next. So any concerns, any safety concerns we haven't discussed, and then the issues that we're asked to specifically comment here? Yes, Dr. Lesar?

DR. LESAR: Yes, this is more of a general comment. I happened to be struck by the differences of some of the things we saw yesterday and the things that we saw today in terms of effect on weight gain, effect on hypoglycemia rates, and effect on end insulin doses.

Now, these may truly be artifacts of the design of the study, but there were some differences that, if one compares, one has to ask themselves is there a best way to dose this combination because we're doing it sort of incrementally. This product used one titration accurate weigh rate and capped at a certain point. Yesterday, they used a slower titration. They saw less hypoglycemia. They saw less weight gain. And they saw relatively lower insulin doses.

So I have a general comment that is probably in relation to the design. But one has to ask themselves, on a more general point of this class of drugs in this fixed ratio, is there a best way to use them and perhaps even what the ratio would be and a way to cap them? So it's a more of a general comment on the restriction of having this combination and that there may be better ways to do things that we just don't know.

DR. SMITH: Dr. Wilson?

DR. WILSON: I'm not too concerned about the GLP-1 agonist as fixed or semi-fixed when you get into the middle range. Obese diabetics, there's more latitude in dosing than we take. The biggest issue is for patients to actually follow through on their programs, to titrate alone.

If they will titrate and it's kept fairly simple, there's only one thing to titrate, the dose, what you dial on the pen. I think we're going to be surprised. I think they're going to actually do quite well. So I'm not too concerned about that.

I have a concern for obese type 2 diabetics. Remember some of our diabetics in the 25 to 65 plus range have a little more brittleness. I do have some concern with that. And Dr. Seely and Dr. Burman might weigh in on that. Somebody for whom a few units of insulin makes a difference, and they're obese, they got 1.5 insulin, we call it in the trade, so to speak. I'd be a little bit concerned about that.

But in general, for most people, I think we're going to be surprised. They're going to do quite well. I do have a little bit of concern about physicians wanting to use the combo therapy in a very heavy patient and then it will lead to some frustration because they'll get to the 60 units and they'll have to stop the product and then start over with a different strategy. So I am a little concerned with the very, very heavy patients.

DR. SMITH: Dr. Seely?

DR. SEELY: So in terms of the inability to dose the two drugs independently, I think that's

one of the things we sacrifice when we get combination drugs. And to me, that's not the big issue as opposed to that we won't know what the patient is taking when they tell us, which is going to go into B.

I think there's, I mean, the fact that it can't give above 60. Maybe eventually the company will make a pen that goes above 60. So there's something available now for people who need 60 or less. So I think, if it's available now for that group of patients, they should get it.

I think the idea of once you hit 60 really sitting and thinking, are you missing something? I mean, it's like a nice time to take pause. I'm not saying everyone would do that. But are you getting pooling of insulin?

As opposed to the person from the company who said it's very rare to ever need to give glargine as a split dose, as a diabetes specialist, that has not been my experience. I have a lot of patients who don't do well on once-a-day glargine and they clearly wear out of their glargine before

the next dose who I split doses on.

So once you hit 60, there may be a lot of considerations about regimens that you might want to consider in any case. So to me that's not a big drawback. And I think, above 60, if the medication and combination works, I'm sure the company will work to develop something that delivers more than 60.

DR. SMITH: Dr. Budnitz?

DR. BUDNITZ: So I don't know if this is a concern as much as just an observation, that for patients who might require just low doses of the combination product, might they have benefited more from just a single dose of a GLP-1 and gotten more weight loss if they had not been started on this combination? And one might never know.

I don't think it's an issue of safety, but maybe it might make perfect management for that individual patient a little bit less likely to happen.

DR. SMITH: Dr. Everett? So, to summarize related specifically to this set of issue in that

first paragraph on the slide, there's been a general sort of consensus that people are not too concerned about issues that arise from the fixed-dose combination.

As discussed in regard to the earlier topics, there's not particular concern about the lower than approved or lower than the effective doses for the GLP-1 analogue and also not a great level of concern about the dose limit of 60 units.

I would add recognizing that a substantial number of patients presumably would be adequately controlled with a dose not exceeding 60 units and, for those that are inadequately controlled with 60 units of insulin, that there will be reasonable ways to deal with that. And so these are not game changers or stoppers in terms of the mix.

Other points beyond that to summarize that people would like to add? So, okay. Now what I'm going to do, I know we're in the middle of a question, but we have kind of a requirement to take a break here. And not for me, but I started it. We'll take the break. So we're going to take a

break.

(Pause.)

So we're going to take a break. It's 3:45. Let's come back here at 4:00. We'll finish discussing this question. I don't want to have to hurry it, so I don't want to do it quickly before the break. And then we'll go on to the voting question.

(Whereupon, a recess was taken.)

DR. SMITH: So I think we'll resume and we're going to discuss the second part of this discussion question. Discuss clinical concerns related to the use of the fixed-combination product which combines a drug that, when used alone, has a wide effective dose range and is titrated to effect on a continuous scale, i.e. insulin glargine, with a drug that, when used alone, has one or two recommended effective doses, i.e. lixisenatide.

If you go to section 2, issues related specifically to product presentation/devices, including but not limited to; use errors that may occur in the care setting related to a lack of

clarity on the amount of each product delivered with each given dose, insufficient understanding that, unlike insulin products, the maximum dose for the combination is capped, inadequate understanding of the role of the two devices.

I know we have some experts in this general area, so maybe we could even get you guys to lead off, Dr. Reed or Dr. Lesar. Dr. Lesar's hand is up. Good.

DR. LESAR: Just a couple of comments. It might be an instance of somebody selecting the wrong drug, whether it's across an electronic environment or the actual physical object. So I have a couple of comments about this.

I'm not too concerned about having two different pens. I mean, we have two different dosage sizes of many drugs. I think it's the clarity of communication in the electronic environment of how these drugs are named and especially with fairly long names with two drugs for which there are two different drug combos. We deal with that all the time about which drug should

be first.

I notice that, on the syringe that's shown, glargine is actually the first drug, but actually glargine, the concentration, is the same between those two syringes. What changes is lixisenatide. And you can't tell that until you read all the way down on the bottom.

Now, I know that's not the final presentation, but it's a good example of something that would be very hard for someone who is going to choose that product to read all those lines and find that's what makes them different. So it wasn't surprising that there was a mistake by a pharmacist in choosing them.

So I think it's important to consider what the naming convention for these combination drugs, what drug, is it glargine, is it insulin first, or is that the GLP-1 first? How do you differentiate the concentrations that are available?

Not just in the physical object, but also in terms of the electronic environment because most prescriptions are going to be written

electronically, what does it look like in an electronic format? What does it look like to the pharmacist when it comes across as electronic? So these things all need to be considered.

I think there will be mistakes made with this pen unless some mitigation doesn't occur to make it clear of what you're trying to express and how it's expressed, again, both in the electronic environment as well in the physical environment.

DR. SMITH: Dr. Meisel, do you have a comment on this?

DR. MEISEL: So I'm very stressed by this issue here with this product in a number of ways. And I think and I'm also distressed. I understand we need to have educational program of 5 million clinicians, but if that's our safety plan, woe to us because we're not going to be able to effectively educate 5 million nurses, doctors, pharmacists, pharmacy technicians to know these products while we've got to engineer these errors out of the system. And I haven't seen anything yet that helps us with that.

I think we know, an endocrinologist will know, and CDEs will know that 30 units of yellow is not 30 units of green. But the nurse taking the history at the nursing home, or on the orthopedic floor in the middle of the night, or the medical assistant doing it in the doctor's office, is going to find out from the patient that she takes 30 units of this drug and the fact that there was two of them. And that there's a difference between yellow and green, other than color, is going to be lost on them. And so I think that's hugely concerning to me.

I think referring to a drug in terms of units and units alone when we have an active drug that's also in micrograms, is problematic because it will set up the mental model that this is just another new funky weird insulin, like we have lots of them out there now.

The people will lose the fact that this is a combination product. They'll see 10 units, 15 units, 30 units, whatever the dose may be, and not be considering the fact that this is not just

insulin. So I think we have to come up with some dose designation that is not strictly 10 units or 20 units, that sort of thing.

I think we talked about before, there isn't another drug on the market today that has that sort of a problem associated with it.

I'm also concerned that we've got a drug delivery device that can deliver doses below which we would consider to be approved. I wasn't satisfied with the response that patients will want to get the last little drop out of the dispenser to save money and supply.

I think that may be valid, but I think that creates a safety problem when we're endorsing, tacitly or not, the notion that you could dial to the wrong color on the scale and say that's okay with a wink and a nod.

I think if the lower dose is X, then we should put a mechanical stop in there so that you can't get anything below X and be done with that. So I think that's an additional problem.

I think I mentioned this earlier, and I'll

say it again. You know, Lantus is commonly given BID. And that may not be the labeling, that may not be the marketing, but that's the real world.

What's going to happen when somebody is on this product and somebody wants to increase it to BID? Do we then end up with what would otherwise be legitimate doses individually out of the pen, 30 and 20, or 40 and 20, or whatever that may be, that while they fit into the design of the pen, the individual dose, but then by doing so we end up overdosing the GLP-1 agent associated with that?

I think we need to give a lot more thought to how to error-proof and engineer that out of the system. And I'm not convinced that the presentation and delivery devices that have been proposed so far get us to that point.

DR. SMITH: Dr. Reed, is this something you would have any further comments beyond these?

DR. REED: No. I mean, I concur with what's been said. I have a little less concern relative to the dose range, an issue that has been brought up by a few. And I'm a little more comfortable

with the two pens, but what Dr. Meisel just brought up clearly in those environments there is risk, and I'd like to hear what Dr. Budnitz has to say about that, based on your experience.

DR. BUDNITZ: So I had another comment. Just remind me what I should address.

DR. REED: Here we have the two different pens, two different doses and plus the flexibility that the user has in dialing dose.

DR. BUDNITZ: So let me think about the flexibility for the user. I'd like to comment. In general, we try to engineer out errors and make it not dependent on folks making the right decision. And so you would do what we call passive engineering prevention interventions, like making it impossible to dial a dose that's too low. So if that's a true safety concern, then the engineering approach is the most effective injury prevention method for doing that, making it impossible to dial lower doses.

I'm going to transition to another medication safety precept, which is

standardization. And I do think this opens up the door, and we should not have duplication of a unit, as Dr. Meisel talked about, to be the units of measure for a product that contains just insulin and a product that contains insulin and something else. So I think it has to be something else. It cannot be units.

Where I would look would be to some standards on units of measure used in medicine, whether it's SNOMED, HL7, even FDA has some standardized units of measure to use. I'd look for one of those that would be appropriate for e-prescribing and computerized order entry.

So I'd work with the vendors because I think one of the issues that was resolved was when someone else who is not the original prescriber has to re-prescribe this. You don't want there to be miscommunications there. I think those are my major comments.

DR. SMITH: Yes, Dr. Stanley?

DR. STANLEY: I was just going to say, about this issue of people getting confused by insulin, I

mean, we've got five or 10 different kinds of insulin. We've got regular insulin, we've got NPH insulin, we've got glargine, and we use units for all of those different kinds of insulin, yet they're clearly totally different in terms of their onset and duration of action.

As diabetologists, we're all totally used to dealing with that. And so when your nursing-home nurse asks what medicine you're taking, you're not saying, "I take 10 units of insulin," or, "I take 10 units of glargine," or, "I take 10 units of regular insulin." And so this is not a totally different scenario.

DR. BUDNITZ: So just to respond briefly, I agree. And actually mixing up insulin doses is the number one most common error that leads to overdose, hypoglycemia, and emergency department visits.

So I think maybe it's a conceptual point, but using units to describe a drug that is not in units, is I think the key difference between this combination product and products that even might be

combination like 70/30 insulin, but still the unit of measure is an insulin unit.

DR. MEISEL: Because it sets up a mental model, people who aren't familiar with this product, that all this is, is insulin, won't realize the fact that this is not just insulin. And they could end up adding Victoza or something to this because they don't even realize what it is that they're using.

DR. SMITH: Dr. Seely?

DR. SEELY: So I think, just from a clinician point of view, working with patients, the way it is currently, if it's called units, it's just a disaster waiting to happen. I think it needs to be given a different term than an insulin unit.

For example, when I give patients growth hormone, most of my patients don't know how much growth hormone they're on, but they know how many clicks they're on and the size of their cartridge. So maybe you'll say, "It's X clicks of," and whatever you pick to call it, it's X clicks of, and

whatever the name is.

But I think I would say, as endocrinologists, we may be used to doing 70/30, but even 70/30, there's different components you can have of that. And during transitions of care, it's a disaster. So when patients are admitted to the hospital on a dose of 70/30, the chance that they're going to get prescribed what they were on is incredibly low.

So I would say the present way we're doing it with all the different insulins, we even need a better way to do. But here, I wouldn't use units, I would pick something else, like clicks of something.

then the other thing I think you have to be really careful about is the color of the pens, because a lot of people are red/green color blind. And sometimes when you're red/green, you may have done testing on this, but things can look yellow. So you really want to be sure that you pick two colors that people, especially aging people who lose macular function and a lot of color

perception -- that the colors are bright enough that people who are color blind can perceive and people who have decreased vision can perceive.

But I actually feel comfortable, as my last comment is, I mean I would feel comfortable with the company and the FDA working out this part.

DR. SMITH: Dr. Wilson?

DR. WILSON: Yes, I agree with Dr. Seely. And I think it would be great to have somebody develop some prototypes to figure out what is best, most easily and accurately communicated to both providers and to patients for a combination product.

Two ideas -- one would be, instead of having one number on the dial, perhaps two numbers with a forward slash between the two numbers or something actually on the pen itself telling you what the doses mean, not in the product insert, but actually on the pen, things like that, but that can be worked out.

DR. SMITH: So yes, FDA comment?

DR. GUETTIER: Yes. So the voting question

asks you to consider the actual device because, actually, the way that we regulate these products is as a total package. So if you actually do not believe that the device is safe, then you have to tell us that in your voting question.

DR. SEELY: But you're saying we can't vote for an approval with that the FDA works this out with the company?

DR. GUETTIER: No. You have to vote on the actual product presentation that's currently proposed today.

DR. SEELY: Thank you.

DR. SMITH: So in that regard, as part of summarizing, what I've been hearing from the group, which I agree with, is that there is not major objection or concern to the notion of this device or these two devices themselves containing this combination of drugs beyond what we discussed in regard to the previous discussion topics.

But there's a lot of concern about the challenges of appropriately labeling, perhaps coloring or structuring the pens themselves, and

communicating in a way that adequately protects against problems that may come from misunderstanding.

We've heard a lot of specific concerns about that, concerns about the fact that the two pens look similar to each other and the color difference isn't great. So for the models we have, this group is not satisfied that that's adequate to adequately support distinguishing.

There's concerns about the labeling and the specifics of that, which we're not in a position to tell you how should be done, but it's somehow very important to be adequately communicating that this is two drugs and it's two agents being given together to more effectively avoid potential confusion of people interpreting this as one agent and specifically as the insulin. There's more work to be done on that.

There's a need to try to address in these labeling issues and use issues not just the pharmacist, and the physician, and the patient, but really all the healthcare providers who may be in a

position to influence what's being done with a prescribed dose of this medication for a patient.

To expand a little on one of those circumstances and as an example, a patient who comes into the hospital who may be using one of these pens, there needs to be some efforts to devise systems that adequately advise the people who will be making decisions on what that patient receives in a way that they know what to do.

And, you know, first of all understanding that this is a two-agent device, then what are they supposed to do? Should they keep using it? Should they lower the amount they're using? Should they take away one and give the other? Depending on the dose in this combination, what dose of insulin should they use? There's a need to wrestle with that and not just let the community figure that out, because that's fraught with hazard. So there's some major labeling issues that really could influence the effective use and the safe use.

So have I left anything major out in summarizing? And I know I added a little emphasis.

DR. MEISEL: Actually, just one additional thought that just occurred to me, if somebody came into the hospital on this stuff and if they came NPO, or on a ventilator, or something, would the recommendation be that they get taken off of this and get put on straight old insulin until they're settled out? I think that needs to be made clear as well.

DR. SMITH: So, again, for the FDA, I think what you're hearing from us is that there's a whole lot of concern about the hazards that come with this combination product. You're not hearing that those are in a sense completely game changers, but it's a real challenge to try to figure out how to do that in a safe manner.

The point was made, which I didn't mention in summarizing, that this is a novel situation. So there aren't other combination drugs like this that people have been using where it sort of fits that pattern. This is a new pattern.

So we're not solving the problem for the FDA and the sponsor, but we're not objecting to the

notion of this construct altogether in this pen, but we're saying that there's at least a consensus at this moment, but we're saying that there's really a challenge here in terms of how to adequately label it, color it, structure it, and then educate the people who are going to be using this or going to interface with it one way or another.

Okay. So we could move, if there's no more comment -- yes, Dan? Dr. Budnitz?

DR. BUDNITZ: Do you mind if I just have FDA clarify a little bit, if we're going to move into the voting question, because there was one comment made about voting that I just want to be clear about.

If we have concerns that Dr. Smith talked about that might be addressed by picking a unit or labeling something on a pen, but it's not done right here in the visuals that we have on these pages, can we make that as a comment? Or do you think that is a voting determination? That's what I just want to clarify before we vote.

DR. GUETTIER: So I think you're going to have to explain your rationale in the vote and hopefully with your rationale you're going to explain why you voted a certain way. And if your vote is contingent on certain things, then please add that contingency to your rationale.

I think my comment was that, you know, this is just one way to present the product. There are other ways to present the product, and, if you think that this way to present the product presents a safety concern for the healthcare setting, then you should obviously --

DR. SEELY: So just to clarify that, I thought the way you answered me was we were voting on this specific device.

DR. GUETTIER: The vote is for this specific device. But if you believe that this device is unsafe, then it should probably color your vote. So, again, it's you're voting on the specific product, which is the entire product, including the pen presentations.

We didn't ask you to opine on labeling

because we don't have a finalized label. But if your vote is, sure this pen is fine, but I want to make sure that this happens in labeling, then we need to hear that in your rationale. But you are voting for this presentation. There's no other presentations.

DR. SMITH: So if we're through with this discussion question, we'll move to the voting question, and we'll come back to make sure we have clarity on this, if we could have the voting question put up.

When we get to the vote, we'll be using an electronic voting system. And so once we activate and begin the vote, the buttons on your microphone will start flashing. They'll continue to flash even after you've entered your vote.

To vote, what you should do is press the yes, or no, or abstain button that corresponds to your vote. If you're unsure of your vote, you can change it while the buttons are flashing and press the one that you want to have pressed.

After everyone has completed their vote, it

will be locked in. The vote will be displayed on the screen. The DFO will read the vote from the screen into the record. We'll go around the room and each person will state their name into their microphone, state what their vote was, and then you can offer what reasons that you might wish to explain your rationale behind your vote.

I would encourage you to not abstain if at all possible. But if it's a difficult choice, I would encourage you to make the choice and then offer your rationale for the choice you made.

So the voting question, based on the data in the briefing materials and presentations at today's meeting, do you recommend approval of the lixisenatide/glargine fixed-combination drug delivered using the proposed pen devices for the treatment of adult patients with type 2 diabetes mellitus?

If you voted yes, explain your rationale and discuss whether use of the combination should be approved for patients not treated with a basal insulin or a GLP-1, for patients who are

inadequately controlled on either a basal insulin or a GLP-1 analog or for both populations. Recommend additional post-approval studies if you think these are needed.

If you voted no, explain your rationale and recommend additional pre-approval studies if you think these are needed.

So before we go to the vote, is there any requests for any more clarifications on how to manage this voting process, and what the question is, and how we should interpret the question? In which case, we can vote.

(Vote taken.)

DR. BONNER: For the record, 12 yes, 2 no, 1 no voting.

DR. SMITH: So I'll just make the point that the no-voting was Dr. Neaton, who had to catch an international flight. We knew that. We wanted his participation in the discussion, which he certainly contributed to, but he simply could not physically be here to make a vote and that's required to participate in the voting process.

So maybe we could start with Dr. Burman. And if you would, in the microphone, state your name, your vote, and then your rationale for your choice.

DR. BURMAN: Sure. Ken Burman. I voted no really based solely on the pen design. Everything else was fine and I'll give more comments briefly in a second. But from the human factors study, 1 out of 15 pharmacists and 1 out of 45 nurses and patients had difficulties with the pen and the device. So I think those can be worked out.

But if I might, Mr. Chairman, let me mention some other aspects. So it could have been a yes with a caveat, but given the comments from the FDA, I felt I had to vote no. But I do think the evidence supports otherwise approval, except for the pen, of this agent as effective and largely safe in the vast majority of patients.

I think the approval and the effectiveness and safety applies to the single agent as well as the combination. It would seem most appropriate to use the combination agent in uncontrolled type 2

diabetic patients who are taking basal insulin or perhaps even a GLP-1 agonist, but we've talked about that before.

It would be difficult to know if a patient required the combination agent if they're only taking oral agent before and the dose may not be adequate. And I think there might be a lower limit on the pen that was talked about before.

There's certainly inherent advantages and disadvantages from a combination product. I think the advantages in this circumstance outweigh the disadvantages except for the one issue with the pen. There are other issues to discuss. They include inflexible fixed ratio, lower doses of liraglutide that may not -- of the short-acting agent which may not be effective, a cap of 60 units of insulin.

The clinical trials may not relate to the real life practice. And there may be difficulty with the algorithm. And there may be difficulty switching to the combination from previous regimens and loss of diabetic control.

I think we need further studies regarding immunogenicity, anaphylaxis and effects of antibody formation on efficacy. And especially focusing on the first two months after beginning of therapy. But those, in my mind, could be post-approval.

The central issues in my mind are, is the short-acting agent, lixisenatide, alone and in combination needed in the healthcare armamentarium to treat uncontrolled diabetes mellitus? My answer is yes. Do the issues raised allow for approval of the product? My answer is yes except for the pen. Do the benefits on A1c overweigh the possible adverse effects? And I think the answer is yes.

I note that there are caveats regarding selective patient groups and ethnic groups, which I don't think were fully studied, and the sponsor said they would want to do that. Patients who require more than 60 units a day are an issue. And the switching agents is something we've talked about before.

In summary, I think there are multiple issues with the agents that need to be considered

and especially the pen. But overall, if used in the appropriate diabetic population, I think it would be a useful agent to help control hyperglycemia and A1c. The pen issues could be addressed by interaction with the sponsor and human factors support. Thank you.

DR. BUDNITZ: Dan Budnitz. I voted yes, but could have been a no. I want to reflect -- I will not reiterate the points that Dr. Burman made. I think they were excellent. I agree with them all. I would just add two points.

One is in terms of approval. The main concern, as I mentioned before, is the potential that some patients may be started on two drugs when one drug would have been effective in some cases. And then I reiterate the labeling concern for the pen for the delivery.

I think it raises a labeling issue for assigning a dose unit, not units of insulin, for what is being administered, whether it's dose steps, or eaches, or whatever. And I do encourage using a standardized vocabulary that does exist or

working with CPOE, any prescribing vendors to come up with what is that best one, along with FDA.

But I do think that these concerns can be addressed, but do need to be addressed as one of the innovative products in this class with the description of a titratable component or at least two components using two different units of measure.

DR. LESAR: Timothy Lesar. I voted yes. Basically, I thought the efficacy in terms of decrease in A1c and decrease in GI side effects balanced some of the risks I was concerned about. Certainly the hypersensitivity reactions can be hopefully monitored with pharmacovigilance post-marketing.

There was some concern about the antibody formation, what the implications of that are, whether that's a class effect or is that drug specific. And I did mention my concerns about the specific dosage form, labeling, and nomenclature that's used.

DR. EVERETT: This is Brendan Everett. I

voted yes. I think the sponsor has demonstrated efficacy of the combination drug in patients on baseline oral anti-diabetic therapy and in patients on insulin glargine. And so I think the primary population where this combination should be approved and really should be directed is amongst those patients who are already taking insulin glargine and who require additional or adjunctive therapy on top of that insulin.

There may be a role, which I think we've expressed some discomfort with, in patients who are not yet on either insulin or a GLP-1 agonist, in particular those where the treating physician senses that it's likely to require significant medications and particular insulin to get them to a hemoglobin A1c range that was optimal.

I also think that the drug may actually be effective at lower doses than those tested in the lixi-alone trials. And I suspect that this is a difficult concept potentially to fit into the FDA's regulatory structure, which is focused on established, existing doses and evidence of

efficacy.

I of course, that's poor conjecture. I don't have data to support that. But my sense is that, in some ways, it's an appealing pathophysiologic paradigm that increasing both of these medications proportionately may actually allow for some benefit. And I think we saw potential mechanisms for that to be the case today with the post-prandial glucose reductions.

Finally, I do have some concerns, as do others, about the delivery device. I suspect and I would say that I voted yes with the idea that I'm not an expert in this and the FDA and the company, who has experience designing appropriate delivery devices, could cross that hurdle. And with that, I will stop talking.

DR. SMITH: I'm Robert Smith. I voted yes. And the major considerations that drove that were that I feel that this combination delivered in this manner, this drug combination meets a clinical need with adequate efficacy.

I think that the safety issues for the most

part are not very concerning, with the exception of some degree of concern about potential allergic reactions.

So that swayed me to vote a yes. I would say that yes is contingent on a few issues. And one of those is to adequately address the concerns that we've heard expressed about the distinction between the two dose devices and then whether by improvements in the color differential or potentially other changes in the physical features, which make them very different from each other, but also through labeling and through instruction materials.

I know that's very challenging, but I would consider that it would be contingent on accomplishing those things adequately. And I would think that that should also include consideration of what could be accomplished and how to address procedural guidance for special circumstances, such as patients who are hospitalized with interrupted nutrition. And so rather than just let people figure out what to do, I think some efforts to

provide guidance for special circumstances would be appropriate.

As part of that, I think that consideration should be given to studying the effectiveness of what evolves as the strategies for labeling and instruction in terms of some sort of formal studies that will actually test their effectiveness or their non-effectiveness as we try to reach something that looks like it's really adequately safe.

I also would strongly suggest, post-approval, if that does occur, that there be monitoring that's adequate in terms of assessing potential serious allergic reactions because I don't think that's adequately resolved yet.

Also, I would give strong consideration to a post-approval -- I would like to see a post-approval study looking at patients who were on a GLP-1 in transition and transitioning to this device. And that may seem like a relatively minor step, but the fact is we don't really have any data on that.

The sponsor has said that they're designing or have designed a study and intend to do that. And I think it would be reasonable to make that a post-approval study requirement because sometimes unexpected things happen, which might inform us either about unexpected adverse things or simply issues related to transitioning, specifics of transitioning.

DR. SEELY: Ellen Seely. I voted yes. I voted yes based on the concept that I think the combination of a GLP agonist and insulin in one preparation so it can be administered in one injection is going to be helpful to patients and to the clinicians who take care of them.

My main hesitancy was the pen. And having the wording of using the proposed pen in the vote was a challenge for me because I feel really strongly that you cannot use the proposed pen, that the pen really needs to be redesigned. You cannot be delivering something that is not insulin as if it's an insulin in units. I think that is really asking for trouble.

When you consider renaming, you need to go through from the patient's home -- from the pharmacy to the patient's home, to the pharmacy, to the hospital, to the nursing rehab, and run through all the scenarios of transition that you'd want to be sure were really clear in terms of distinguishing the dose that you're giving as well as which pen the person's using.

In terms of the post-approval studies, I think it was well expressed that what you have shown us is that if you go through nothing/metformin onto your combination, people do well. And if you go from insulin onto your combination, people do well.

But as Dr. Smith mentioned, we don't have the data that, if you go from GLP-1 analog onto a combination, you do well. And if that's going to be one of the groups that you're going to recommend this for, then I think you need the data.

The group that I would market it most for, from my point of view, is people who are already on insulin who are needing to add something. But I

think there's enough variability in patients that there should not be any limitation in the approval.

So in addition to the GLP with then transition to the combination, I agree with Dr. Smith that there really needs to be careful vigilance to looking at allergies. There appears to be different allergenic responses to some of the GLP-1 agonists that are already on the market. Maybe the studies are not great. But there may be different immunogenicity because of the structures of the molecules, despite them having the same receptor activities or similar binding. So I think the allergic reaction part really needs to be worked out well post-marketing.

MS. HALLARE: Diana Hallare. I voted yes because the studies, although preliminary and might have been small in sample, showed that the pen was relatively safe and/or not too difficult to use.

As a few other panelists have mentioned, the population for which this combination may be more preferable is for those who are not naïve to basal

insulin or GLP-1 agonist. And also this combination showed that it produced no or little increase in hypoglycemic events.

DR. MEISEL: Steve Meisel. I voted no, and it seems like we'd have more consensus if we had categories said yes if, or no unless. Then we'd have more consensus on this because I think we're more or less in agreement on lots of these things.

I think the combination clearly is at least medically safe and effective for the populations that we've been talking about here today. I do hear the concern about the lack of data for people on the GLP-1 and adding to this, I mean common sense would say it would be effective, but we don't have the data to prove that. And if you want to market something for something, you've got to have some data to prove that. So I have that concern.

I also have a concern about the weight-based piece of this. If you have somebody who is 300 pounds or something and you know their insulin requirement is going to be real high, are there some limits beyond which we shouldn't be thinking

about this? And that may not be a package insert approval question, but it should be a guidance kind of question.

I think the concerns about allergy, I would just echo without belaboring it. The issue about presentation, I had mentioned most of my concerns just a few minutes ago. I won't belabor those.

But I'll go back to the BID once-daily issue on this. As we talked about earlier, if the individual drug ends up being used BID, because it's pharmacologically -- and the data seems to show that it's more effective on a BID basis, what would happen if we're converting from a person who is on BID lixi to this product?

How would that then create some new challenges for the combination so that we don't do this in a way that ends up overdosing on the wrong product? And I think that needs to be thought out as well. And I think all the other elements of my concerns I said before and so I won't belabor.

DR. WILSON: Peter Wilson. I voted yes. Most of the possibilities for different ways to

interpret on how to vote have already been voiced, and so I won't reiterate those.

But I think one of the things that's not been mentioned -- and patient groups and advocacy groups spoke about this -- is this provides yet another choice. And similar to other GLP agonists and combinations with insulin, we may have more than one. So I think choice is very important for physicians and for patients.

The other thing that I see coming is an educational campaign for providers and for patients. And one of the biggest barriers we have is better control of diabetic patients. And that means getting most effective treatments. And perhaps it's not been studied. That's why I will state it.

Endocrinologists, we do not have enough of, at least in the United States or other places, and this ought to be easier to accomplish for the internist and family practitioner to bridge to insulin plus yet another agent for effective glucose lowering. This is really simple compared

to some of the regimens we use in endocrinology. And it's incumbent upon the sponsor to make this easier for the doctors.

I have confidence they'll work out the delivery system. And I think this will be a boon for patients. I really do. I share Dr. Seely's, Dr. Smith's, and Dr. Burman's -- I think all of us want to see some further information, especially on taking insulin or a GLP-1 agonist and then adding the combination. I think that's where endocrinologists especially will want to see more science as we move forward.

DR. STANLEY: This is Charles Stanley. I voted yes. I think, by this time, we've gone around the table so far there's not a whole lot to add. I think there's good evidence of efficacy and the safety profile is reasonable. And clearly, for the patients, the possibility of a single injection using a combination that addresses both fasting glucose and post-prandial glucose is very attractive.

I think the issue about the device has

mostly to do with what we're going to call the milliscrimpeur [ph] of whatever it is we're injecting. And maybe one way of avoiding that is not to think about this as units of insulin or micrograms of GLP-1, but as volume of whatever it is you're injecting.

The company really has two different drugs. One is labeled yellow and one is labeled green, and you give a volume, 10 microliters or 60 microliters, and that's your dose. And then somebody will have to have a little app to translate that back into more common units, but that might be one way of avoiding the safety issues.

DR. YANOVSKI: Susan Yanovski from NIH. I voted yes, although with less than complete enthusiasm. I think that the sponsor showed they met their targets for efficacy. And I think the safety is generally consistent with the class effects. I do think that the potential for serious allergic reactions needs to be tracked closely post-marketing.

I believe it should be used primarily in patients who are already on a basal insulin or a GLP-a receptor agonist. However, I really was disappointed that we did not have data showing the use of iGlarLixi as an add-on to patients who were already on a GLP agonist. And I'd like to see those studies done post-marketing.

I also think that the insulin cap in the comparator studies really limited my confidence in its superiority over insulin. Also given the high percentage of patients who have diabetes who have severe obesity, I'd also like to see studies using the product in patients with a BMI over 35.

MS. BERNEY: I'm Barbara Berney, and I'm the patient representative, and that is how I am approaching my vote. I did vote yes, but I concur with all of the things that have been -- all of the concerns that have been raised. I am particularly concerned about the packaging and delivery of the medication.

But I also want to make a comment about the units business. This apparently is the wave of the

future, so somewhere pretty quickly we need to figure out how we're going to describe whatever it is, because I think the concern that people are going to say unit, oh, insulin, because even I, as a patient, think unit, insulin.

So I think they're all legitimate concerns, but for the same reasons that some of you have commented, it is another weapon in the fight. And it is a fight. The ease of use will probably induce better compliance. I would hope so, because even I, who am very compliant, messed up on the all-day-long thing. The convenience of the one injection daily makes a huge difference to a patient, especially somebody who is working, and doesn't have a place to store insulin, and all of those things.

The other concern that patients have, of course, is the weight gain. And as I mentioned yesterday, I gained 30 pounds in 2.5 months. How much of that was the prednisone, how much of that was the insulin is something to be seen, but I quit because my blood pressure went up. I felt awful.

And the idea that this would maintain or even help a diabetic to lose some weight would be good.

I do think that the sponsor has shown that is effective control of A1c and blood glucose. And with what appears to be, for the drug itself, an adequate safety profile.

DR. REED: This is Michael Reed. I voted yes. I struggled with my decision. And I thought very hard what Jean-Marc said. And I took it from the positive slant that I can vote yes with contingencies. And much of that has already been described, but I feel strongly about a number of issues.

One is, as Dr. Everett brought up, I think on a molecular level, mechanistically, pathophysiologically, this combination makes a lot of sense. I think it may, who knows, it has an opportunity to even change a paradigm. We're not there yet. So that is what really led me to more on to approve this product.

But I have major concerns about the units, and it's been brought up. And I appeal to the FDA,

this isn't the first. It's not the last. We have got to come up with some kind of naming convention or some standardized way of labeling the dose in some way that it is standardized and we can all appreciate.

I struggled tremendously with the device. I think Dr. Seely and others have brought up some very good comments of coloring and how that may affect individuals with sight problems, color blindness, et cetera. But I don't really have a problem with two different devices.

I don't have a problem with is this too low of a dose, because again we're looking at a combination product, and the dose response relationship of that compound was shown clearly at 12.5 and up. So I don't feel too concerned about that.

I feel concerned about the confusion in dosing and how it may be confused. As we saw in a very small study, the pharmacist dispensing the wrong one.

I also have concerns over allergy. And I

would suggest to the agency that a post-marketing surveillance, some type of specific study looking at allergy would be important. As a clinical investigator, I appreciate the best we can do in designing well designed studies. I think the sponsor did very good studies, et cetera.

But you know what, it doesn't -- we can't always control for that. There is something on this radar -- there may be something on this radar screen. And when you look at it relative to just other drugs, these numbers, even as they were adjudicated, the question behooves us to look and see, is there something more to this as we go forward.

But I also feel that choice, cost, and convenience was factoring into my decision. But I have concerns over the device, the naming, the dosing convention, and the allergy.

The last thing I would say, Mr. Chairman, is I, like probably everybody here, would be very interested on an academic level on the antibody relationships, but I think that may be a more

academic pursuit early on. But I would embed that with any further studies.

DR. NASON: My name is Martha Nason, and I voted yes, but, like almost everybody here, I don't have much to add. I will repeat a little bit what other people have said. I'll try not to kick a dead horse too much.

But like most of my colleagues, I do believe there's a place for this. I believe efficacy was demonstrated. This could be appropriate and useful for a group of people, probably mostly people who are already taking insulin and interested in starting GLP-1. And for those people, I think it would be very convenient, possibly cost effective -- I can't really speak to that -- and a good option to have on the table at least.

Like my colleagues, I think safety issues have mostly been addressed. I do still hesitate not only about the allergic reactions, but about the antibody status and the FDA's concern about cross-reactivity. That still makes me nervous and I don't really know. I'm sort of glad it's your

job and not mine to try to figure that out because, pre-marketing or post-marketing, it seems very complicated.

It seems like, if there is some cross-reactive effect, other than seeing a decrease in efficacy, if it's something that would go on to affect somebody later down the road, maybe even after they stopped taking the product because of decreased efficacy, that would be nearly impossible to figure out.

So I'm concerned about it but I don't know what to do about it. Certainly try to follow people long term, but I don't know that you can even follow people after they stop taking the drug as well.

I certainly agree with the questions of confusion with the two pens and the units and that, that needs to be worked out. I don't have anything to add above what my colleagues have said who are much more familiar with that.

So just as a last note, the post-approval studies, I do think it's necessary, as other people

have said, to look at folks already on GLP-1 who want to add insulin if that is a target audience. I do think the long-term question of allergy, and antibody, and reactogenicity would be important.

I think, as I think one of our patient representatives mentioned, this should be studied, looked at in more non-white people as well. The numbers there were pretty small, and future studies, too, but hopefully some post-marketing information there and especially in African-Americans. Some of the other racial groups were a little better profiled, but there were very few African-Americans across the whole set of studies.

DR. SMITH: Dr. Kewalramani is the industry representative. You don't vote, but do you have any final comment you might want to make?

DR. KEWALRAMANI: I think that the areas of concern and improvement for the packaging have been well described. Maybe I'll just end by saying as Uncle Ben said to Spiderman, with great powers come great responsibility, and with great innovation comes responsibility to take the next step to

figure how to appropriately label this combination product and make sure that patients have access to it in a safe manner.

DR. SMITH: And FDA, is there any final comment you might like to make?

DR. GUETTIER: So I'd like to thank the applicant and the FDA presenters. There's a lot of work that goes into these presentations beforehand. So thank you for great presentations today. I'd like to thank the panel for sitting here for 2 days and for your thoughts on very complicated issues.

I'd like to maybe put a plug in for all the other powers that be for. At least what's apparent is that it's very difficult to make a decision when we don't have the data. And for some of the questions that we ask, it would have been nice to know what strategy is actually beneficial.

So if we already knew from the get-go that being aggressive had some tangible benefit for patients in the long run, it would be more easy decisions to make, but we don't have that data.

So thank you all for your thoughtful

comments today and yesterday.

Adjournment

DR. SMITH: And I would also like to thanks the panel for your hard work and very helpful comments and interactions, the FDA for helping us with the data and guiding us through this process as well. And the sponsor, when it felt stressful, which it always does, did a great job of putting the data together, and presenting it, and dealing with our questions. And we do appreciate that as well.

I'd like to thank the open public hearing speakers for your input, which really does matter in this process.

So remind the panel members, please take all your belongings with you because you're leaving this room until the next time you come for one of these meetings. And turn in your registry badges to the registration desk. And so this meeting is adjourned.

(Whereupon, at 4:56 p.m., the meeting was adjourned.)