FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC)

Tuesday, May 24, 2016

8:00 a.m. to 4:47 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. SMITH: So good morning. I would like to first remind everyone to please silence your cell phones, your smartphones, any other devices that make noise if you haven't already done so.

I'd also like to identify the FDA press contact, Theresa Eisenman. Theresa, if you're present, would you please stand? In the back, in the middle there is Theresa Eisenman.

My name is Robert Smith. I'm the chairperson of the Endocrinologic and Metabolic Drugs Advisory Committee. I'll be chairing this meeting. I will now officially call the Endocrinologic and Metabolic Drugs Advisory Committee meeting to order.

We'll start by going around the table introducing ourselves and I think we'll start with the FDA to my left here and come around the table.

DR. PARKS: Good morning. I'm Mary Parks.

I'm the deputy director in the Office of Drug Evaluation II.

DR. GUETTIER: Jean-Marc Guettier, division director of the Division of Metabolism and Endocrinology Products, FDA.

DR. YANOFF: Lisa Yanoff, clinical team leader, Division of Metabolism and Endocrinology Products, FDA.

DR. CONDARCO: Tania Condarco, medical reviewer, Division of Metabolism and Endocrinology Products.

MS. KETTERMANN: Anna Kettermann, statistician in the Office of Biostatistics.

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. COOKE: David Cooke. I'm the interim director of Pediatric Endocrinology at Johns Hopkins.

DR. NEATON: Jim Neaton, biostatistics, School of Public Health, University of Minnesota.

DR. LESAR: Timothy Lesar, director of Pharmacy, Albany Medical Center, Albany, New York.

DR. EVERETT: Brendan Everett, director of In-Patient Cardiology at the Brigham and Women's Hospital and Harvard Medical School, Boston.

DR. BONNER: LaToya Bonner, Designated Federal Officer for this meeting.

DR. SMITH: And I'm Robert Smith. I am professor of medicine and endocrinology and also a professor of public health at The Medical School and at Brown University.

DR. GELATO: I'm Marie Gelato. I'm professor of medicine in the Division of Endocrinology at the State University of New York at Stony Brook.

MS. HALLARE: Diane Hallare, Consumer Representative.

DR. MEISEL: Steve Meisel, Patient Safety Officer, Fairview Health Services in Minneapolis.

DR. WILSON: Peter Wilson, professor in

medicine and endocrinology, preventive cardiology, epidemiology at Emory University.

DR. STANLEY: Charley Stanley. I'm a professor of pediatrics at University of Pennsylvania, School of Medicine and pediatric endocrinologist at Children's Hospital of Philadelphia.

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

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

DR. REED: Good morning. I'm Michael Reed. I am director of the Clinical Research Center and I'm a clinical pharmacologist, toxicologist at Rainbow Babies and Children's Hospital, University Case Medical Center in Cleveland.

DR. NASON: Good morning. I'm Martha Nason. I'm a mathematical statistician at the National Institutes of Allergy and Infectious Diseases.

DR. KEWALRAMANI: Reshma Kewalramani. I'm

the industry representative and the head of the U.S. medical organization 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 of 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 LaTonya 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 Drug 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 government 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 discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as

well as those imputed to them, including those of their spouses or minor children and, for the 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, royalties; and primary employment.

Today's agenda involves a discussion of the safety and efficacy of New Drug Application 208583 for insulin degludec and liraglutide injection submitted by Novo Nordisk Incorporated for the proposed indication adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.

This is a particular matters meeting during which specific matters related to Novo Nordisk's NDA 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 statements 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 discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships

that they may have with the firm at issue. Thank you.

DR. SMITH: Okay. 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. My name is Jean-Marc Guettier. As I said before, I'm the director of the Division of Metabolism and Endocrinology Products at the FDA.

I would like to begin by welcoming members of the advisory committee to today's meeting, which is convened to discuss a new fixed-combination drug submitted by Novo Nordisk for the treatment of adults with type 2 diabetes.

Over the next 10 minutes, I'll walk you through some of the regulatory and clinical issues that were raised by this application. So the product in this application is a combination drug.

Let me review the regulatory framework for combination drugs. The purpose of this review is to provide you with important background

information that pertain to today's discussion.

The Food and Drug Administration's policy on fixed-combination drugs is defined in Title 21 of the Code of Federal Regulations. The regulation on combination drugs states that two or more drugs can be combined in a single dosage form when each component makes a contribution to the claimed effect.

Thus, a combination drug that has an effect versus 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've just heard, the rule refers to claimed effects. And for an antidiabetic combination drug, the specific topic of today's discussion, the claimed effect is improvement in glycemic control captured using HbA1c changes.

As most members of this committee know, demonstration of an improvement in glycemic control over placebo is currently considered a validated

surrogate of clinical benefit by the agency for the purpose of approval of antidiabetic drugs.

For fixed combinations of antidiabetics, 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 the two drugs co-administered is greater than the glucose-lowering effect of each individual drug.

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 comparator.

This scenario assumes that the first drug is

still contributing an effect when the second drug is added.

Although both types of studies could 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 dose of a first drug.

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

As was seen in the program that will be discussed today, at least some patients in all trials were able to reach glycemic control goals on

a single agent. Whether the patient would respond to a single agent is unknown when deciding to recommend single versus dual therapy.

Having covered the contribution to claimed effect concept, I am 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 combination product; 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 an 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 rational.

The second question on the slide addresses the regulation itself and refers to the reality of the combination product. It asks whether the proposed dosage offered in the combination 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 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.

Let's now turn to the proposed product in this application. The proposed combination in this application combines two already approved and marketed active pharmaceutical ingredients referred to as drug substances; degludec, a basal insulin injection once daily, and liraglutide, a glucagon-like peptide-1 receptor agonist also injected once daily.

As was stated in the previous slide, a legitimate question for any combination product is, does combining these two active ingredients make clinical sense?

In concept, combining the two active ingredients in a single dosage form 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 requiring 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, this is a decision left to the practitioner. Nevertheless, for the purpose of addressing the discussions at today's meeting, you will 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 an oral agent and a regimen including either a GLP-1 receptor agonist and a basal insulin, only patient already using both or all of the above?

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 these may restrict the clinical utility of the product for a specific population of patients requiring concurrent therapy.

Would it be reasonable, for example, to select an insulin-sensitive patient population who would only require low doses of the product since, at these doses, patients may be receiving a dose of one of the component that is not contributing to the effect?

Alternatively, in a population with severe insulin resistance, the dosage in the combination may be insufficient to provide long-term control because higher doses of insulin then can be delivered by the combination product will be required.

The applicant has proposed the following populations in the studies they have conducted for the combination product application. These are: patients not previously treated with either an insulin or a GLP-1 receptor agonist who have failed

a first-line agent, patients inadequately controlled on a basal insulin, or patients inadequately controlled on a GLP-1.

So once more, the combination rule states that the dosage of each component 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 limitations of a fixed-combination product administered using the proposed device would satisfy this aspect of the regulation.

The figure compares doses of liraglutide and degludec drug substances in Victoza and Tresiba, the marketed liraglutide and degludec drug products approved for the treatment of type 2 diabetes, two of the doses of a fixed-combination product to propose in this application.

The first thing to note is 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.

You can also appreciate from the figure that Victoza, the liraglutide drug product approved for type 2 diabetes, is not dosed on a continuous scale as is proposed for the combination product but as two discrete dose steps.

You should know that doses of liraglutide below 1.2 milligrams were not indicated for the treatment of type 2 diabetes because efficacy was not demonstrated in this range.

You should also know that doses above 1.8 milligrams were not indicated for the treatment of type 2 diabetes because the maximal glucose lowering effect for liraglutide was achieved at a dose of 1.8 milligrams.

You can appreciate from the figure that for a significant part of the liraglutide dose range in the combination product, subjects will be exposed to doses of liraglutide that were not demonstrated

to be effective.

You can also note that the approved effective dose of 1.8 milligrams is reached only when the maximum insulin dose is reached. It will be important to consider how these limitations would affect how you would use this product.

For example, is it reasonable to keep patients on low doses of the combination product for months without knowing whether the benefits of this component outweigh its risks?

In patients inadequately controlled on but tolerating a maximally effective dose of liraglutide, does decreasing the dose make sense if you believe liraglutide is still exerting an effect?

Finally, Tresiba, the degludec 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 50 units. How would this limitation impact concurrent use?

So the areas highlighted in red or

non-overlapping areas and areas we view as problematic for this product. So the central issue raised by this application is: Do 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 population requiring concurrent use?

So this concludes my introductory remarks and the committee is charged with discussing and opining on whether the product administered using the proposed device would be safe and effective for a significant patient population requiring concurrent use 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 deliberations.

I'll now turn to the discussion and voting questions.

So in the first discussion point, we ask you to discuss the benefits of starting two drugs at once in patients with type 2 diabetes mellitus not

treated with either a basal insulin or a GLP-1 agonist. And that's two drugs administered using the fixed-combination product.

In the clinical care setting, you have a range of options for these patients and one option is to start one of the two component agents. So we'd like to know why you would start two drugs at once in these patients and what benefits you are targeting with this strategy versus a strategy that relies on adding drugs sequentially.

Keeping in mind the issues of dosing, please describe the patient population in whom you would recommend this product.

Discussion point number 2, in the second 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 then again keeping in mind some of the limitations of the dosing, we are asking you to opine on who would be a candidate for the

fixed-combination drug and why.

Discussion point number 3, in the third 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 one or two recommended effective doses.

In this discussion point, you can also discuss any concerns that are not raised in the other discussion points. But we would like you to specifically address the following issues:

Issues related to loss of dosing flexibility, including but not limited to some of the examples in the question and then issues related specifically to product presentation.

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

device for the treatment of patients with type 2 diabetes.

If you vote yes, please provide your rationale in the recommended patient population for whom you would recommend the product and recommend additional post-approval studies if you think these are needed.

If you vote no, please again provide your rationale for voting no and recommend any additional pre-approval studies that you view as needed.

This concludes my 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 is 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 interest in a sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, the 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.

So we'll now proceed with Novo Nordisk's presentations.

Applicant Presentation - Robert Clark

MR. CLARK: Good morning, Mr. Chairman, members of the committee, FDA colleagues, and all participants here today. My name is Robert Clark. I'm vice president of Regulatory Affairs for Novo Nordisk in the United States.

Novo Nordisk is here today to review our new treatment for patients with type 2 diabetes, IDegLira.

The medical community is faced with the unfortunate reality that the prevalence of type 2 diabetes is increasing at a rapid rate around the world.

Despite the abundance of treatment options, most patients aren't reaching their A1c goals. And getting the goal is important because it decreases the risk of long-term complications.

It's been clearly established that effective control of type 2 diabetes improves patient outcomes. In fact, the ADA recommends that a patient's A1c goal should be below 7 percent and AACE recommends a goal of less than or equal to 6.5 percent.

IDegLira represents an important advance over currently available treatment options. Today, we'll present data showing that IDegLira is a novel combination product that is highly effective at lowering A1c.

It has a well-characterized safety profile and it provides patient-centric therapy in people who require intensification with a simple once-daily injection.

IDegLira is a co-formulation of two FDA-approved diabetes treatments, the GLP-1 receptor agonist liraglutide whose trade name is Victoza and insulin degludec whose trade name is Tresiba.

Liraglutide and insulin degludec had been extensively studied in separate comprehensive clinical development programs for the treatment of diabetes. And the individual components are used together clinically in the real world.

IDegLira, the treatment for which we are seeking FDA approval, has been previously approved in 34 countries worldwide, including in Europe. Novo Nordisk has conducted a thorough clinical development program for IDegLira involving nearly 3500 patients.

The rationale of combining these two agents was to take advantage of their complimentary modes

of action. Insulin degludec lowers blood glucose in a dose-dependent manner.

Its pharmacokinetic profile includes a long duration of action, allowing it to be dosed once per day, and it produces its glucose lowering effects with low day-to-day variability.

The GLP-1 receptor agonist, liraglutide, lowers glucose only when levels are elevated and it targets both fasting glucose and post-meal glucose peaks. It's also dosed once a day.

By combining a basal insulin and a GLP-1 receptor agonist, we target both fasting plasma glucose and post-prandial glucose, which provides better efficacy than either of the individual agents alone. IDegLira also mitigated some of the side effects seen with the individual components.

We designed the clinical development program for IDegLira to align with the FDA's requirements for combination products, specifically that the combination product has superior efficacy relative to its individual components and that each component contributes to the total efficacy

observed.

Our full program included five phase 3 trials in patients most likely to use IDegLira. After discussion with FDA and to meet these regulatory requirements, we designed two pivotal trials in patients with inadequate glycemic control, assessing the contribution of each component in the combination.

Three additional trials extended the evaluation of IDegLira in different patient populations likely to receive benefit from this therapy.

In our presentation today, you'll see data that demonstrate that IDegLira was highly effective. These efficacy results were both clinically relevant and statistically significant versus comparators.

We've clearly established that each component of IDegLira contributes to the product's efficacy and this efficacy was seen across a broad dose range.

In our two pivotal trials, between

60 to 80 percent of patients reached an A1c of less than 7 percent at the end of therapy and these reductions were greater than that seen with the comparators. This efficacy was maintained for up to 52 weeks in our largest trial.

IDegLira mitigated some of the common side effects of each component when dosed individually and it was well tolerated. And as I mentioned, the individual components are already used together clinically in the real world.

Our proposed indication for IDegLira is for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. IDegLira is recommended for treatment intensification in patients with type 2 diabetes and is not for initial therapy.

IDegLira, whose proposed trade name is Xultophy, is a single daily injection in 3-mL prefilled multi-dose pen, delivering dose increments of 1-unit insulin degludec and 0.036 mL liraglutide.

There are demonstration pens on the table in

front of you, no needles attached to the pen so the demonstration pen will not actually dispense any drug.

In designing this pen, we considered the patient's perspective and we created a pen device and education materials that are patient-centric. When IDegLira is prescribed, the patient will simply dial the prescribed dose on the pen.

For example, this slide shows an IDegLira pen for a dose of 10, where the number displayed on the dial represents the patient's prescribed dose. Please note that the pen that we intend to market cannot deliver a dose higher than the maximum recommended dose of 50.

I'd now like to take you through the agenda for the rest of our presentation this morning. Dr. Christopher Sorli will discuss the rationale for new treatment options for patients with type 2 diabetes.

Dr. Stephen Gough will provide a summary of the efficacy data for IDegLira from our clinical development program. Dr. Todd Hobbs will then

summarize the safety data for IDegLira and Dr. Gough will return to conclude our presentation by describing the benefit-risk considerations for this treatment.

I would now like to introduce Dr. Christopher Sorli, chair of the Department of Diabetes, Endocrinology, and Metabolism at the Billings Clinic in Billings, Montana.

Dr. Sorli was an investigator in our clinical program, and he's acted as a consultant to Novo Nordisk, and we are compensating him for his time and travel.

Applicant Presentation - Christopher Sorli

DR. SORLI: Thank you, and good morning. I'm pleased to be here today to discuss the rationale for a new treatment in type 2 diabetes and how it can help us better manage our patients.

There is an evolution occurring in how we, as clinicians, are treating our patients with type 2 diabetes. The new standard of care is helping patients identify and reach their individualized A1c targets.

In addition, we must help them overcome the treatment barriers that have prevented appropriate intensification of therapy. So I will discuss why a co-formulation of a basal insulin in a GLP-1 receptor agonist is an effective approach to achieve these new treatment goals.

Now, as we all know, there has been a dramatic increase over the last decade in the number of people diagnosed with type 2 diabetes and in the number of people at risk for developing diabetes.

Today, more than 22 million adult Americans or over 7 percent of the population are diagnosed with diabetes. Over the last decade, novel research, clinical practice experience and an expanded repertoire of treatment options have helped us better understand and address the complexity of this condition.

Individualized treatment guidelines based on outcome data are now supported by ADA and AACE. And their recommendations of A1c targets of less than 6.5 or 7 percent come with an important caveat

that achieving this goal is done safely.

ADA guidelines explicitly focus on avoiding hypoglycemia while AACE guidelines recommend avoiding both hypoglycemia and weight gain as these are important factors that contribute significantly to intensification barriers and to patient morbidity.

So how do we, as clinicians and patients, determine individualized goals and risks? We now have guidance, including this ADA paradigm. And this is a tool that I use in clinic every day to help me guide patient care.

It assesses individual patient characteristics to guide how aggressively we set glycemic targets. For example, for a patient very early in the disease without comorbidities who is motivated, my A1c target is less than 6.5 percent.

Now, alternatively, an A1c target of greater than 7.5 percent is appropriate for a patient with long-standing disease, multiple comorbidities, and limited access to diabetes education.

Getting patients to goal is important

because outcome studies have clearly demonstrated a strong correlation between improvements in glycemic control and microvascular outcomes such as retinopathy, neuropathy and kidney disease.

Results are less clear with regards to macrovascular complications. And some long-term studies of intensive glucose control suggest that getting patients to goal early can have long-term benefits in reducing cardiovascular disease and mortality while other studies in patients with increased risk of cardiovascular disease suggest that intensive control may negatively impact mortality.

Fortunately, we now have a variety of therapies to help us individualize treatment for type 2 diabetes, including the ability to combine therapies.

For the vast majority of patients, diabetes is a progressive disease. And to maintain targets, we often need to intensify treatment. For patients not at their goal, intensification options include adding another oral agent or the injectable options

of a GLP-1 receptor agonist or basal insulin.

As our discussion today involves a co-formulation of GLP-1 receptor agonist and basal insulin, I would like to specifically focus on these therapeutic options.

Both basal insulin and GLP-1 receptor agonist are highly effective at lowering glucose and yet we are not maximizing their full potential. In randomized controlled trials, on the left, fewer than half of patients taking a GLP-1 receptor agonist achieved A1c levels less than 7 percent.

The results in insulin-treated patients are similar or even more disappointing. Only 30 percent of insulin-treated real world patients from the NHANES database achieved A1c target.

So why are we not being more successful with these two individual therapies? Because intensification via up-titration of a single therapy in a complex disease presents barriers that can lead to clinical inertia.

These barriers and the inertia they generate inhibit our ability to intensify treatment and to

help patients reach their goal. In the case of insulin, while recognized as perhaps the most effective agent to lower blood sugar, clinicians and patients have a well-documented inertia.

Intensifying insulin therapy leads to increased risk of hypoglycemia and weight gain. For GLP-1 receptor agonists, also potent glycemic agents, we're hesitant to initiate or to intensify because of nausea and other GI side effects.

But given that the glucose lowering mechanisms of these two agents are complimentary, there is a rationale for combining them in an intensification strategy that could enhance efficacy and overcome barriers.

Patients with diabetes have altered regulation of multiple hormones within the complex regulatory system that controls glucose and energy. For most patients, intensification of a single agent is incapable of effectively addressing this complexity.

An optimal treatment strategy would target multiple components of the underlying

pathophysiology. Specifically, a combination of a GLP-1 receptor agonist and basal insulin will impact many of the known abnormalities underlying type 2 diabetes.

Such a combination makes good sense from a physiologic treatment perspective, but its application in clinical practice continues to present challenges.

Using both drugs together would require patients to take more injections. And we know from clinical practice experience and peer-reviewed literature that more injections translate into decreased adherence, reduced compliance, and less patient satisfaction.

In addition, healthcare providers may be unsure about how to select the proper starting dose of each of the individual therapies, how to add one of these therapies to the other, and how to safely titrate each medicine independently.

So a co-formulation of a basal insulin and GLP-1 receptor agonist would allow both agents to be administered in a single injection. An approved

co-formulation would establish a safe and effective initiation in titration algorithm based on fasting glucose.

In addition, a co-formulation would help to minimize the delays we currently see in achieving glycemic targets due to the sequential addition of one therapy to another and would accomplish this while avoiding uncertainty regarding titration of individual components.

Therefore, a co-formulation of GLP-1 receptor agonist and basal insulin will provide these practical and clinically important benefits while simultaneously providing a pathophysiologic-based treatment strategy.

During my 25 years in clinical practice, I have witnessed an evolution in how we are treating our patients with type 2 diabetes. Protocol-driven strategies of a decade ago have given way to strategies of prevention and disease modification that can and should be individualized.

A combination of a GLP-1 receptor agonist and a basal insulin will provide a treatment

capable of addressing complex pathophysiology in a single injection and an easily understood titration algorithm.

This tool would be an important part of our evolving treatment strategies to get more patients safely to their individualized goal.

Thank you very much for your attention.

Applicant Presentation – Stephen Gough

DR. GOUGH: Thank you, Dr. Sorli.

My name is Stephen Gough, senior principal clinical scientist at Novo Nordisk and a practicing endocrinologist with a specialty in diabetes.

I will present data today showing that IDegLira provides the clinical benefits of the basal insulin, insulin degludec, and the GLP-1 receptor agonist, liraglutide. And it does this in a once-daily injection, using a simple starting dose and titration algorithm.

These data will show that IDegLira met the primary and key secondary endpoints in all of the phase 3 trials. In addition, the IDegLira combination was superior to each of the individual

components and each of the components contributed to A1c reduction across the entire dose range.

IDegLira also produced a greater A1c reduction than basal insulin and GLP-1 receptor agonists. Finally, a high proportion of patients achieved an A1c of less than 7 percent in all trials. In our largest study, up to 80 percent of patients reached this target.

The clinical trial program was designed to deliver a number of objectives. The first was to meet regulatory guidance and demonstrate the clinical benefit of IDegLira over each of its individual components: insulin degludec and liraglutide.

The second objective was to assess the contribution of each component to A1c lowering across the entire IDegLira dose range.

The third was to evaluate IDegLira across the spectrum of people with type 2 diabetes. This included people with inadequate glycemic control on different background therapies.

The phase 3 program evaluated nearly 3500

people with type 2 diabetes in 28 countries. Two pivotal trials, 3697 and 3912, were designed to meet FDA regulatory guidelines for the development of a combination product by demonstrating clinical benefits of IDegLira over its components.

Trial 3697 was designed to demonstrate the superiority of IDegLira over liraglutide alone. Trial 3912 was designed to demonstrate the superiority of IDegLira over insulin degludec alone.

Three additional trials expanded the investigation of IDegLira in different clinically relevant populations with type 2 diabetes and also versus different comparators.

All trials were 26 weeks in duration. And the largest trial, 3697, included a 26-week extension to provide 52-week data.

We developed IDegLira as a fixed-ratio combination. A maximum IDegLira dose of 50 can be delivered in a once-daily injection, providing 50 units of insulin degludec and 1.8 milligrams of liraglutide.

This takes into consideration the 1.8-milligram per day maximum liraglutide dose approved for type 2 diabetes.

A key feature of IDegLira is its simple standardized starting dose. People on OAD therapy initiated IDegLira at a dose of 10, providing 10 units of insulin degludec and 0.36 milligrams of liraglutide. This dose was selected to reflect the usual starting dose of basal insulin in this population.

People converting from basal insulin or a GLP-1 receptor agonist started IDegLira at a dose of 16, providing 16 units of insulin degludec and 0.6 milligrams of liraglutide. This starting dose reflects the established higher insulin requirements of this population.

Notably, in the clinical trial program, patients could administer IDegLira at any time of the day.

Another important feature of IDegLira is its simple titration algorithm, which was consistent across all trials. The dose was adjusted by an

increase or decrease of 2 of IDegLira.

This was determined by self-measured fasting glucose to achieve a target of 72-90 milligrams per deciliter. This ambitious titration target was in alignment with our insulin degludec development program, where we achieved statistically and clinically meaningful reductions in A1c.

Patients performed the titration twice weekly based on the average of the preceding three days' fasting glucose levels.

If the patient was above target, they increased by a dose of 2 of IDegLira. If below target, they decreased by a dose of 2 of IDegLira. When the patient was at the fasting glucose target, no changes were made. Trials with basal insulin as the comparator also used this titration algorithm for basal insulin.

In Trial 3951, we set a slightly higher upper fasting glucose target of 108 milligrams per deciliter. This was to decrease the potential risk of hypoglycemia for people on sulfonylurea therapy.

We used the same endpoints and statistical

approach in all trials to ensure consistent analysis of data.

The primary endpoint, namely the change in A1c from baseline, and the key secondary endpoints shown on this table were consistent across the program.

We adjusted the analyses of body weight and confirmed hypoglycemic episodes for multiplicity when IDegLira was compared to basal insulin with no maximum dose cap. This is designated with the letter M in the table.

For the comparison to degludec in Trial 3697, we also included analyses of insulin dose and post-prandial glucose as multiplicity adjusted endpoints.

We used last observation carried forward as the pre-specified primary approach to impute missing values. Recognizing that this methodology has its limitations, we conducted multiple sensitivity analyses, which are described in your briefing book.

These analyses included a repeated

measurements analysis, two multiple imputation methods mimicking intension-to-treat scenarios, and a tipping point analysis. Furthermore, the analyses were repeated for the protocol and complete analysis sets.

In presenting the efficacy results, I will first show results from the two pivotal trials that demonstrate the clinical benefits of IDegLira relative to its components, liraglutide and insulin degludec, and the contribution of each component to IDegLira across the dose range.

Then I will summarize the efficacy results for all five trials, including the three additional trials in people on commonly used background therapies and versus different comparators.

I'll begin with the two pivotal trials. We designed the largest trial, 3697, to specifically demonstrate insulin degludec's role in the clinical benefit of IDegLira.

The second pivot trial, 3912, was designed to specifically demonstrate the contribution of liraglutide to glycemic benefit.

Trial 3697 evaluated people with type 2 diabetes uncontrolled on all antidiabetic agents. The primary hypothesis was to superiority in A1c reduction with IDegLira versus liraglutide and non-inferiority versus insulin degludec. We assessed additional clinical benefits of IDegLira versus insulin degludec through secondary analyses.

Trial 3697 was an open label, parallel-arm study in which patients were randomized to IDegLira, insulin degludec alone, or liraglutide alone in a 2 to 1 to 1 ratio.

Liraglutide was escalated to 1.8 milligrams per day over two weeks. Insulin degludec and IDegLira doses were titrated twice weekly based on the self-measured fasting glucose. There was no upper limit on the insulin degludec dose.

All patients were taking metformin with or without pioglitazone at randomization and continued taking these agents during the trial. Their baseline A1c values were between 7-10 percent. You can find a full list of inclusion and exclusion criteria in your briefing book.

The primary endpoint was assessed at 26 weeks. At that point, all patients were offered to continue on their randomized therapy and enter a 26-week extension phase. This provided a total of 52 weeks of data.

In this largest pivotal trial, 3697, the demographic and baseline characteristics of the study population were representative of people with type 2 diabetes. And the characteristics for people on IDegLira were well matched to the individual components.

The mean age was around 55 years and about half of the study participants were women. The mean baseline A1c for all three groups was 8.3 percent.

The mean BMI was in the obese range, around 31 kilograms per meter squared. The mean duration of diabetes was around 7 years and included people who have had diabetes for over 50 years.

About one-third of patients were from the U.S. Efficacy results for the U.S. population are similar to the total population and are provided in

your briefing materials.

At 26 weeks, more than 88 percent of patients had completed the trial in the IDegLira and degludec arms and more than 82 percent in the liraglutide arm. Most patients in all treatment groups continued into the extension phase and completed the 52-week study.

IDegLira met the primary endpoint and provided significantly greater reductions in A1c at week 26 compared to insulin degludec or liraglutide.

Degludec reduced A1c by 1.44 percent and liraglutide reduced it by 1.28 percent. This was compared to IDegLira, which reduced the A1c by 1.91 percent.

As you will hear later from Dr. Hobbs, the benefit of the lower A1c value with IDegLira compared to insulin degludec was also associated with a lower rate of hypoglycemia.

At week 26, the primary analysis time point, patients taking IDegLira achieved a mean A1c level of 6.4 percent. And they maintained this level at

52 weeks at the end of the extension phase.

Patients on IDegLira achieved these lower A1c levels with a significantly lower daily insulin dose compared with degludec. As a reminder, IDegLira and insulin degludec doses were titrated using the same protocol-based on self-monitored blood glucose values.

These glucose values, shown on the top graph, declined through 12 weeks, then stabilized at similar levels in both groups.

The daily insulin dose is shown below at each time point during the trial. The IDegLira dose stabilized by week 12, but the insulin degludec dose, required to achieve and maintain the fasting glucose target, continued to increase from baseline.

This trend persisted through week 52, at which time people in the IDegLira arm were taking around 23 units less or 33 percent less insulin than the degludec-only arm.

The briefing document shows that the end-of-trial equivalent liraglutide dose is also

lower with IDegLira than with liraglutide alone.

More than 80 percent of patients taking IDegLira reached the target A1c value of less than 7 percent at week 26. And 70 percent reached the target of less than 6.5 percent.

For both targets, the proportion of patients who reached goal was higher with IDegLira than with either component, and all odds ratios were statistically significant in favor of IDegLira. The right-hand panel shows that a similar percentage of patients reached their A1c goal at week 52.

As you have seen in your briefing book, sensitivity analyses supported the results of the primary analysis of change in A1c. This slide shows sensitivity analyses for A1c at week 26 and includes the forest plots for the estimated treatment difference for IDegLira versus degludec on the left and versus liraglutide on the right.

The top row shows the primary analysis using the predefined LOCF method. Below are the results of the sensitivity analyses. These confirm the

robustness of the findings.

The tipping point analysis, provided in your briefing document, further confirm the robustness of the primary analysis results.

Now, let's look at each component's contribution to efficacy across the dose range. While the starting dose for liraglutide monotherapy is 0.6 milligrams and 1.2 milligrams is the lowest approved maintenance dose, we explored whether doses lower than 1.2 milligrams had an effect when titrated as part of IDegLira.

As this was a treat-to-target study, we can compare the change in A1c across a range of dosing requirements. Patients were divided into three end-of-trial post-randomization dose groups with patients on IDegLira in blue and insulin degludec in orange.

Those on the left of the slide were taking an IDegLira dose of less than 16, which is equivalent to 0.6 milligrams of liraglutide, the recommended starting dose for liraglutide alone.

The middle group represents patients

requiring an IDegLira dose of more than 16 but less than 32, which is the equivalent to 1.2 milligrams of liraglutide, the lowest recommended maintenance dose of liraglutide alone.

The final group on the right were on a dose of more than 32 units of IDegLira. Within each group, more patients on IDegLira achieved a target A1c of less than 7 percent than those on insulin degludec alone.

The A1c reduction was greater. This includes those on IDegLira doses of less than 16 or 32. Importantly, this occurred with similar daily mean, end-of-trial insulin doses within each group. This analysis supports liraglutide's contribution across the entire dose range.

The change in fasting plasma glucose supports the self-measured glucose results that I've already shown. The reduction in fasting plasma glucose with IDegLira was similar to that with degludec, but significantly greater than that with liraglutide.

The improvement in fasting plasma glucose at

26 weeks was maintained at 52 weeks. Fasting glucose was stable from week 12 to week 52 and, as I showed you previously, was associated with significantly lower and stable A1c values with IDegLira compared to insulin degludec.

In addition to improving the fasting glucose, IDegLira also significantly improved post-prandial glucose compared with degludec alone. To evaluate the post-prandial glucose effect, we used two methods in a pre-planned subgroup: a standardized meal test and continuous glucose monitoring.

In the standardized meal test, all groups had similar post-prandial glucose excursions at baseline. This is shown in the panel on the left. Plasma glucose concentrations are plotted on the Y-axis at time points up to 240 minutes following the test meal.

At week 26, shown on the right, IDegLira reduced post-prandial glucose relative to insulin degludec with a significantly lower normalized incremental area under the glucose curve.

As you can also see, the beneficial post-prandial effect of IDegLira was similar to that seen with liraglutide. These observations were confirmed over three meals during a 24-hour period using continuous glucose monitoring.

As you heard from Dr. Sorli, weight gain can be a barrier to adequate blood glucose management and lead to suboptimal dose titration with basal insulin.

In Trial 3697, patients taking IDegLira achieved significantly better glycemic control than those taking degludec. And importantly, as shown in the blue curve, they did it without weight gain.

Patients in the degludec group, shown in orange, gained weight over the 52-week trial extension period while those on liraglutide, in green, lost weight. These observations indicate that the liraglutide component of IDegLira helped mitigate the basal insulin-associated weight gain.

The second pivotal trial, 3912, was designed to specifically demonstrate the contribution of liraglutide to glycemic benefit in people with

type 2 diabetes already on basal insulin therapy.

The study was designed to demonstrate superiority of IDegLira over insulin degludec. It was a double-blind, parallel-arm study in which patients were randomized to IDegLira or insulin degludec in a 1 to 1 ratio.

The IDegLira starting dose was 16. Patients in both arms of the trial were titrated to the same fasting glucose targets. But the insulin degludec arm was capped at a maximum of 50 units.

This was done so that the maximum possible insulin degludec dose allowed matched the maximum IDegLira dose of 50 so that we could demonstrate the contribution of the liraglutide component.

The demographics, disposition and the complete secondary endpoint data are in your briefing document.

The top graph shows that both treatment groups achieved equivalent doses of insulin degludec shown by the superimposable curves. In the bottom panel, the A1c curves separate with time and the A1c reduction at week 26 was superior with

IDegLira compared to degludec.

IDegLira met the primary endpoint of this study. The A1c treatment difference was 1 percent in favor of IDegLira, producing an end-of-trial A1c of 6.9 percent.

Importantly, at equivalent insulin doses, the IDegLira group achieved better glycemic control. This confirms that liraglutide contributed to A1c lowering in the IDegLira group.

Taken together, the two pivotal trials, 3697 and 3912, met their primary endpoints, meeting regulatory guidance and confirming the clinical benefit of IDegLira over each of the components, insulin degludec and liraglutide. We also demonstrated a glycemic benefit across the dose range of IDegLira.

Regarding secondary endpoints for which analyses were adjusted for multiplicity, IDegLira improved post-prandial glucose relative to basal insulin, reflecting the effect of liraglutide.

IDegLira achieved significantly better glycemic control at a lower insulin dose than with

unrestricted degludec dosing. We saw no weight gain with IDegLira compared to degludec alone in patients in all antidiabetic treatment.

We also observed significant weight loss compared to basal insulin in patients already on basal insulin therapy and significant reduction in fasting glucose versus liraglutide, although not adjusted for multiplicity.

Importantly, the effects on A1c and weight in our largest pivotal trial were preserved throughout 52 weeks.

The key results from the other phase 3 clinical trials in the IDegLira program were consistent with the results from the pivotal trials.

I will summarize results for patients uncontrolled on OADs, basal insulin and GLP-1 receptor agonists.

Sulfonylureas are frequently used in people with type 2 diabetes. Therefore, in Trial 3951, we evaluated IDegLira in an OAD therapy population as an add-on to existing sulfonylurea therapy.

This was a double-blind, parallel arm study in which patients were randomized to IDegLira or placebo in a 2 to 1 ratio. We initiated IDegLira at a dose of 10 and continued sulfonylurea therapy and metformin in both treatment arms.

Shown here is the change in A1c when IDegLira was added on to sulfonylurea therapy. Compared to sulfonylurea therapy plus placebo, IDegLira reduced A1c by 1 percent. This was statistically significant and met the primary endpoint of the trial.

The change in A1c with IDegLira in patients on metformin with or without pioglitazone from Trial 3697, which excluded sulfonylureas, is shown here. Taken together, the two studies demonstrate the efficacy of IDegLira across a broad range of oral agents.

Moving on to the weight results, in Trial 3951, there was a weight gain with IDegLira and a weight loss with placebo on a background of sulfonylurea therapy. The end-of-trial 1.5-kilogram difference between IDegLira and

placebo was significant.

Again, to remind you, we saw no weight gain when IDegLira was added to metformin with or without pioglitazone in Trial 3697. These results indicate that IDegLira was associated with little weight change in patients on existing OAD therapy.

Trial 3952 extended the investigation of IDegLira to people uncontrolled on metformin and a pre-trial insulin glargine dose of up to 50 units. In contrast to study 3912, which I've already presented, Trial 3952 imposed no upper insulin dose restriction.

This design allowed insulin glargine to be freely titrated against the fasting glucose and was intended to more closely resemble normal clinical practice.

This was an open label parallel-arm study in which patients were randomized to IDegLira or insulin glargine in a 1 to 1 ratio. The patients randomized to IDegLira started at a dose of 16 while patients randomized to insulin glargine started the trial at the pre-trial insulin dose.

The same titration algorithm that I described previously was used. All patients continued with metformin therapy.

We observed a significantly greater reduction in A1c with IDegLira compared to insulin glargine at week 26. The end-of-trial treatment difference in A1c was 0.59 percent in favor of IDegLira. This met the primary endpoint and confirmed the glycemic benefit of IDegLira over basal insulin therapy alone.

We next evaluated the insulin doses and self-monitored fasting glucose in these patients. In the top panel, we see that IDegLira achieved the A1c benefit at a lower insulin dose relative to the insulin glargine group.

At week 26, patients in the IDegLira group required around 25 units or 38 percent less insulin compared to insulin glargine. The A1c and insulin dose results occurred in the context of essentially equivalent self-monitored glucose levels shown in the lower figure.

This is important for several reasons.

First, when patients enter the trial and switch from insulin glargine to an IDegLira dose of 16, there was, on average, no deterioration in glycemic control.

Second, the self-monitored blood glucose-based dose titration algorithm was successful. It also illustrates that fasting glucose levels were stable over the final 12-14 weeks of the trial.

Finally, the results support a liraglutide contribution to the glycemic efficacy of IDegLira. Overall, these data support the greater A1c lowering and insulin sparing effects of IDegLira over basal insulin.

Turning now to changes in body weight, in study 3952, change from baseline and body weight was adjusted for multiplicity. The insulin glargine group gained weight while the IDegLira group lost weight. The 3.2-kilogram end-of-trial difference was statistically significant.

In keeping with the data from Trial 3912 shown as a reminder, we observed a weight benefit

with IDegLira compared to basal insulin in people with uncontrolled type 2 diabetes on basal insulin therapy.

Trial 3851 investigated the switch from GLP-1 receptor agonist therapy to IDegLira. The population included people taking one or more OAD and a GLP-1 receptor agonist at maximally tolerated dose.

This was an open-label, parallel-arm study in which patients are randomized to IDegLira or continued GLP-1 receptor agonist therapy in a 2 to 1 ratio.

Eighty percent were on liraglutide and 20 percent on exenatide. Patients randomized to IDegLira started at a dose of 16, delivering 16 units of degludec and 0.6 milligrams of liraglutide.

IDegLira demonstrated superior A1c reduction when compared with GLP-1 receptor agonist therapy continued at a maximally tolerated dose. Again, IDegLira met its primary endpoint.

As shown on the left, the week 26

end-of-trial treatment difference was 0.94 percent. Shown on the right, a weight loss of 0.8 kilograms occurred with continued GLP-1 receptor agonist therapy while a mean weight gain of 2 kilograms occurred with IDegLira.

In addition, there was no deterioration in the self-monitored blood glucose values with the switch from GLP-1 receptor agonist therapy to IDegLira.

To briefly summarize the three additional studies, IDegLira demonstrated a superior reduction in A1c versus comparators. These included placebo in patients on existing sulfonylurea therapy, unrestricted up-titration of basal insulin glargine, and continued GLP-1 receptor agonist therapy.

IDegLira was associated with weight gain compared to placebo in patients on sulfonylurea therapy and weight gain compared to unchanged GLP-1 receptor agonist. In contrast, IDegLira was associated with a weight benefit compared to basal insulin glargine.

Finally, I will summarize the glycemic response to IDegLira in all five trials. Across the clinical trial program, a greater proportion of people with type 2 diabetes reached the A1c goal of less than 7 percent with IDegLira.

Among patients uncontrolled on OAD therapy, almost 80 percent achieved an A1c of less than 7 percent in two clinical trials. When we compared IDegLira to basal insulin, we also saw a significant difference.

In study 3912, 60 percent of patients reached the glycemic target on IDegLira compared to 23 percent for those on the maximum degludec dose of 50 units.

In study 3952, 72 percent of patients achieved targets on IDegLira. This is compared to 50 percent reaching target on insulin glargine where there was no maximum dose applied.

Finally, in study 3851, 75 percent who switched from a GLP-1 receptor agonist to IDegLira reached the 7 percent A1c goal. This is compared to 36 percent of those who remained on their

pre-trial GLP-1 receptor agonist at a maximally tolerated dose.

In all studies and relative to each comparator, the odds for achieving the target were statistically in favor of IDegLira.

To summarize, the pivotal trials designed in accordance with regulatory guidance demonstrated the clinical benefit of IDegLira over its individual components, insulin degludec and liraglutide.

All five clinical trials met their primary endpoints, showing greater reductions in A1c for IDegLira versus comparators in people with type 2 diabetes, uncontrolled, on pre-trial, OAD therapy, basal insulin therapy or GLP-1 receptor agonist therapy. And each component contributed to this effect.

Across our program, more people with type 2 diabetes achieved target A1c with IDegLira than with comparators. In the largest study, 80 percent of patients reached the A1c goal of less than 7 percent.

The glycemic effects included significant reductions in fasting glucose relative to liraglutide and post-prandial glucose relative to basal insulin.

Compared to the use of basal insulin IDegLira achieved superior glycemic control with the need for lower total daily insulin doses. I have also shown that IDegLira mitigated the weight gain observed with basal insulin.

Finally, IDegLira achieved these results using a simple starting dose and titration algorithm.

I would now like to ask Dr. Hobbs to present the safety information from the development program and then I will conclude with our benefit-risk assessment.

Applicant Presentation - Todd Hobbs

DR. HOBBS: Thank you, Dr. Gough, and good morning.

The individual components of IDegLira are FDA-approved and have been used extensively around the world. There are now more than 5 million

estimated patient years of exposure for liraglutide and more than 300,000 estimated patient years for degludec.

Our clinical trial program demonstrated that the safety profile of IDegLira is consistent with those of the individual components. And it mitigates some of the key side effects of each individual's therapy. These include the risk of hypoglycemia compared to basal insulin alone and GI events when compared to GLP-1 receptor agonists alone.

We pooled data from the five phase 3 trials in our clinical development program into four groups to facilitate comparison among treatment groups. These groups included patients who are on IDegLira, patients on basal insulin including degludec and glargine, patients on a GLP-1 receptor agonist including liraglutide and exenatide, and patients on placebo.

When presenting the pooled safety data, I will show the adjusted frequencies and rates to account for differences in trial designs, mostly

variances in randomization ratios and background therapy.

An external independent committee blinded to treatment adjudicated pre-specified events of interest including cardiovascular events, suspected pancreatitis cases, neoplasms, thyroid disease resulting in thyroidectomy, and all fatal events.

These events were identified by the investigator through reports of medical events of special interests or by predefined MedDRA searches among all reported AEs.

I, first, will present the general safety of IDegLira, followed by the safety events of special interest. These are based on identified and potential risks of the individual components of IDegLira.

Overall, a similar percentage of patients experienced an adverse event or a serious adverse event in the IDegLira treatment group compared with basal insulin, GLP-1 receptor agonists and placebo.

Specifically, when reviewing the AEs leading to withdrawal, the higher proportion of patients on

GLP-1 discontinued treatment due to AEs compared to IDegLira and basal insulin treatment groups.

Looking at the adverse events in more detail, the most frequently reported AEs included illnesses that occur commonly in the general population. These include headaches, nasopharyngitis and upper respiratory tract infections. Also included were GI adverse events, which are known to be a class effect of GLP-1 receptor agonists.

IDegLira-treated patients had a lower incidence of the GI events, nausea, diarrhea, and vomiting as compared to the GLP-1 receptor agonist group. However, patients on IDegLira had a higher incidence of these same GI events when compared to basal insulin.

Moving on to serious adverse events, overall, the incidence of SAEs was low and similar among groups, and no event occurred in more than 1 percent of patients.

There were no apparent patterns or clustering events in any active treatment group.

And we observed no treatment-related trends for SAEs leading to study discontinuation, dose reduction or temporary withdrawal of trial product. Your briefing book provides more details on the serious adverse events.

Most AEs leading to withdrawal were GI-related and a lower proportion of patients in the IDegLira group discontinued when compared to the GLP-1 receptor agonist group. No single event led to the discontinuation of more than 2 percent of patients in any treatment group.

In the clinical trials, there were four fatal events: three in the IDegLira group and one in the basal insulin group.

Two of the events in the IDegLira treatment group and one event in the basal insulin group were adjudicated to be cardiovascular in nature. Further details of the death are included in your briefing book.

Turning now to the safety events of special interest, starting with hypoglycemia, in the IDegLira program, hypoglycemia was defined

according to clinically relevant and accepted criteria.

Severe hypoglycemia was defined using the current ADA definition, that is, an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

All cases recorded as severe hypoglycemia events were reviewed by an endocrine specialist, blinded to treatment, to ensure that the events were classified accurately.

The category of confirmed hypoglycemia includes severe hypoglycemia episodes along with episodes of hypoglycemia, having a plasma glucose less than 56 milligrams per deciliter, regardless of symptoms.

We also evaluated the ADA-defined documented symptomatic hypoglycemia, which included symptomatic hypoglycemia episodes with the self-measured plasma glucose of less than 70.

There were 12 events of severe hypoglycemia across the entire trial population and the rates

appeared to be similar across treatment groups. All patients who experienced a severe hypoglycemia event fully recover.

Looking at the rates for confirmed hypoglycemia in the three trials with insulin as a comparator, the rate of confirmed hypoglycemia was lower with IDegLira than with basal insulin.

Across these trials, patients on IDegLira experienced a confirmed hypoglycemia rate, 32 to 57 percent lower than those on basal insulin.

These lower rates with IDegLira occurred concurrently with greater improvements in glycemic control compared to basal insulin as seen by the end-A1c values below each trial.

We conducted a similar analysis using the ADA documented symptomatic definition of hypoglycemia of less than 70. And even with this less stringent definition, we saw a similar reduction in the rates of hypoglycemia with IDegLira compared to basal insulin alone.

GLP-1 agents carry a very low risk for hypoglycemia when used alone. So we were not

surprised to see that combining basal insulin with liraglutide increased the hypoglycemia rate over that of a GLP-1 receptor agonist alone.

This trend was significant for IDegLira compared with liraglutide in Trial 3697 or with unchanged GLP-1 receptor agonists as the comparator in Trial 3851.

The rate was also higher with IDegLira when compared to placebo in patients taking a background of metformin and sulfonylurea therapy in Trial 3951.

Now, to review GI events, these are known class effect of GLP-1 receptor agonists but not of insulin, so we anticipated seeing a GI event rate intermediate between insulin and GLP-1 receptor agonists.

Here, we see the percent of patients experiencing nausea over the 52 weeks in Trial 3697. This trial enrolled patients naïve to GLP-1 therapy and was open label in design.

The incidence of nausea with IDegLira was lower than that with liraglutide alone, but higher

than that with insulin degludec. Nausea was most prominent during the first four weeks, occurring in up to 11 percent of patients on liraglutide versus less than 3 percent on IDegLira. Nausea rates with insulin degludec were very low throughout the 52 weeks.

We saw a similar nausea incidence with IDegLira in the double-blinded studies and with a higher IDegLira starting dose. Shown here is the proportion of patients reporting nausea in Trial 3912, which had an IDegLira starting dose of 16.

The percentage of patients reporting nausea with IDegLira was similar to that in Trial 3697 and the results were comparable for the IDegLira group and the insulin degludec group.

As we heard from Dr. Sorli, the incidence of GI events is important because these events often lead patients to discontinue treatment. The results of Trial 3697 illustrate this point.

In Trial 3697, GI events leading to withdrawal were less frequent with IDegLira than

with liraglutide. The flattening of this cumulative plot shows that most withdrawals occur during the first six weeks with liraglutide-treated patients.

Now to review pancreatic safety, all GLP-1 receptor agonists carry information describing increased cases of pancreatitis in their labeling based on post-marketing surveillance reporting an association of these events and pancreatitis.

Both the FDA and the European Medicines Agency, or EMA, reviewed the safety surveillance data and concluded that a causal relationship between GLP-1 receptor agonists and pancreatitis or pancreatic cancer cannot be confirmed.

It is important to mention that patients with a history of pancreatitis were excluded from the IDegLira clinical program and, if pancreatitis was confirmed during the trial, patients were to be withdrawn.

In the IDegLira clinical trials, no pancreatitis events were confirmed by the external adjudication committee in patients on IDegLira,

basal insulin, or placebo groups.

Two events of acute pancreatitis were confirmed in patients assigned to GLP-1 receptor agonist treatment. As part of our pancreatic safety monitoring, we also measured lipase and amylase levels throughout the trials.

Both levels increased in the GLP-1 and IDegLira groups, consistent with changes historically observed with GLP-1 receptor agonists. The mean values for IDegLira patients remained in the normal range. And in the absence of other signs and symptoms, elevations of pancreatic enzymes alone are not predictive of acute pancreatitis.

In the IDegLira program, there were three cases of adjudicated confirmed pancreatic cancer, one in each treatment group. None of the patients reported symptoms or signs at study entry and all had advanced metastatic disease at the time of diagnosis.

Looking at cardiovascular safety, the IDegLira program included people with low or

moderate cardiovascular risk and was not designed as a cardiovascular outcomes program. As expected, we saw a very low number of major adverse cardiac events, or MACE, across the program.

In addition to collecting and analyzing MACE, we assessed the cardiovascular safety of IDegLira by reviewing other measures that could affect CV outcomes such as blood pressure, heart rate, ECG changes, and cardiac biomarkers.

The cardiovascular safety data from the individual component development programs is informative for this program. And it is important to note that the individual components of IDegLira are being studied in dedicated CV outcomes trials.

MACE data from the liraglutide diabetes program excluded a 1.8 relative CV risk. LEADER, the outcomes trials for liraglutide, is a post-approval requirement conducted to meet FDA's 2008 guidance regarding CV risk assessment for new type 2 diabetes medications.

This randomized, double-blind, placebo-controlled study compares the

cardiovascular safety of liraglutide to placebo in patients with type 2 diabetes and high cardiovascular risk.

The data from LEADER are still being fully analyzed and we will provide the results to the FDA for their review later this year.

The CVOT for insulin degludec known as DEVOTE was designed in conjunction with FDA to establish the CV safety of degludec. DEVOTE is a randomized, double-blind study in over 7,000 patients with type 2 diabetes and high CV risk comparing insulin degludec to insulin glargine.

The interim results from DEVOTE were part of the basis for the approval of degludec in the U.S. last year. The trial is ongoing and the interim results have been disclosed only to the data monitoring committee and a small group responsible for the interim analysis report.

As I mentioned earlier, an external independent committee, blinded to treatment, adjudicated pre-specified cardiovascular events in

the IDegLira program.

Events identified as cardiovascular events by investigators were sent for adjudication. In addition to those events reported directly by the investigator, we performed a broad MedDRA search for terms possibly cardiovascular in nature. This was to ensure we captured all potential MACE for external adjudication.

The same standard three-component MACE definition was used in all trials. This included nonfatal myocardial infarction, nonfatal stroke and cardiovascular death.

Shown here are the MACE events by treatment group. There were 15 MACE events in 15 patients across the program of nearly 3500 study participants; 10 events occurred in patients on IDegLira, 4 events in basal insulin patients, 1 in a GLP-1 patient, and none in the placebo group.

In order to further define the CV safety of IDegLira, we evaluated other parameters that are important for the cardiovascular health of patients with type 2 diabetes.

GLP-1 receptor agonists are associated with 2- to 3-beat per-minute increase in heart rate. In order to evaluate IDegLira's effect on heart rate, we can look at Trial 3697, where patients were naïve to GLP-1 agents or insulin.

In this trial, the effect with IDegLira in blue is similar to that with liraglutide in green. Degludec alone had no consistent effect on heart rate.

GLP-1 receptor agonists have been associated with small reductions in systolic blood pressure. In the IDegLira clinical program, systolic blood pressure decreased from baseline to week 26 in all treatment groups.

The effects in the GLP-1 receptor agonist and IDegLira groups were similar. In contrast, we saw a neutral or lowering effect of IDegLira on systolic blood pressure compared to basal insulin as shown in Studies 3912 and 3952.

We saw no clinically relevant change in diastolic blood pressure in any of the treatment groups. In addition to these effects on blood

pressure, IDegLira also exhibited beneficial effects on both lipids and cardiac biomarkers.

People with type 2 diabetes have been shown to have a higher incidence of certain types of neoplasms. As I mentioned previously, all cases of suspected neoplasms were adjudicated by an external committee blinded to treatment.

Here's a summary of the treatment-emergent EAC-confirmed neoplasms. Overall, there were 16 patients reporting neoplasms in the IDegLira group; 4 patients on basal insulin, 4 on GLP-1, and 1 in a patient placebo group.

In addition to these treatment-emergent neoplasms, there were two additional non-treatment-emergent neoplasms reported in patients in the IDegLira group.

One was a pancreatic carcinoma in a patient who had advanced disease early in the trial and the second was a localized breast carcinoma in a patient who completed Trial 3697 before the diagnosis was made.

We will monitor ongoing IDegLira clinical

trials, as well as the individual component CVOTs when available to gather additional information about neoplasms.

Now, let's review the thyroid disease information. All long-acting GLP-1 receptor agonists carry a labeled warning related to C-cell tumors including medullary thyroid carcinoma.

This warning is based on the finding of C-cell tumors in rodent studies with liraglutide. Liraglutide is currently part of an ongoing U.S. registry to track cases of MTC.

In the IDegLira program, we evaluated thyroid safety through adverse event reporting, event adjudication, and also through calcitonin measurements.

In the phase 3 trials, there were no reported cases of thyroid C-cell tumors including medullary thyroid carcinoma, nor were there any treatment-related trends observed in serum calcitonin levels. And once approved, we will include IDegLira into the established MTC registry.

Because IDegLira is new combination product,

it's important to review medication errors that occurred during the clinical program. Overall, there were few medication errors and no differences among treatment groups.

The most common errors were patients dialing above the maximum dose of 50. And as you heard, this will not be possible with the marketed pen. Importantly, these errors did not lead to any serious consequences in the trials. In addition, in the countries where IDegLira has been approved, our pharmacovigilance activities have not detected any medication error signal.

To summarize the safety data, the IDegLira safety profile was consistent with the known safety profiles of the two FDA-approved drugs, degludec and liraglutide.

The combination of the two components mitigated some of the common adverse effects of basal insulin and GLP-1 receptor agonists when used alone.

We saw consistently lower rates of confirmed hypoglycemia with IDegLira compared to basal

insulin. And as expected, we saw higher rates with IDegLira than with GLP-1 receptor agonists and placebo.

IDegLira reduced the incidence of GI events versus GLP-1 receptor agonists alone but the incidence was higher than with basal insulin alone. There were no confirmed cases of pancreatitis in the IDegLira group.

The cardiovascular safety of IDegLira appears reflective of the safety of each of its components and it's important to remember that available clinical trial data supported FDA approval of each component. And no cases of MTC were reported with IDegLira. Overall, the safety profile of IDegLira reflects the safety of the individual components.

Lastly, I would like to review with you our proposed post-approval activities and our risk mitigation plans. Our post-approval plan will build upon the risk mitigation strategies already in place for both insulin degludec and liraglutide.

For medullary thyroid carcinoma, we have a

registry and a REMS communication plan and IDegLira will be added to this registry. Pancreatitis is also addressed in our REMS, as well as in a medical claims database study that collects data on pancreatitis and neoplasms.

As I mentioned earlier, dedicated cardiovascular outcomes trials will provide definitive assessments of CV safety for insulin degludec and liraglutide, as well as additional long-term safety data for the individual components.

We're also developing programs to ensure that healthcare professionals, pharmacists, and patients use IDegLira appropriately. The program for healthcare professionals is similar to the one implemented in Europe, where IDegLira has been in use for over 12 months.

It will include information on how IDegLira should be administered, the starting dose, dose adjustments, and how to report adverse events and medication errors.

We will use multiple avenues including our

diabetes educators in our sales force, a professional website and emails, electronic modules and videos, peer-to-peer medical education programs, and participation in relevant professional meetings.

We will provide educational information similar to this for pharmacists, yet specifically targeted for those professionals to inform them about the use of IDegLira.

For patients directly, we will implement a communication plan that will consist of email and direct mail communications to support compliance and persistence. In addition, the product website will provide patients with important safety information and detailed instructions on how to use IDegLira. Together, these activities will help to ensure that IDegLira is used properly and by the appropriate patients.

Dr. Gough will now return to summarize the benefit-risk profile and conclude our presentation.

Applicant Presentation - Stephen Gough

DR. GOUGH: Our presentations today have

summarized key data showing that IDegLira represents an advance in treatment for diabetes with a favorable benefit-risk profile.

Our study showed that IDegLira achieved statistically significant and clinically meaningful improvements in glycemic control. This impressive efficacy was consistent across all trials and within a diverse group of patients on a range of therapies.

IDegLira also has a well-characterized safety profile that is aligned with its individual components. Importantly, we achieved all of this with a once-daily injection and with a simple algorithm for initiating and titrating treatment.

IDegLira is indicated for people not adequately controlled on current therapy. In other words, they need treatment intensification. In light of this, we must balance the benefit-risk profile of IDegLira against other options to intensify therapy, including GLP-1 receptor agonists and basal insulin.

First, let's look at the benefit-risk as an

alternative to GLP-1 receptor agonists. IDegLira has the advantage of greater A1c lowering and gets more patients to goal. IDegLira also has the advantages of greater fasting glucose-lowering and fewer withdrawals from gastrointestinal side effects.

The higher rates of hypoglycemia and lesser weight benefit relative to GLP-1 receptor agonists may give them an advantage over IDegLira in some patients.

The ongoing risk management activities for the components will be applied to IDegLira. This assessment illustrates that IDegLira has a favorable benefit-risk profile relative to GLP-1 receptor agonists for patients needing treatment intensification.

Moving now to IDegLira's benefit-risk in patients who are choosing between IDegLira and intensified basal insulin, in this setting, IDegLira has the advantages of greater A1c lowering and gets more patients to their target A1c than basal insulin.

IDegLira also has the advantages of greater post-prandial glucose lowering, less hypoglycemia, and less weight gain. However, basal insulin may have an advantage in patients who are worried about the GLP-1 class effects. The ongoing risk management activities for the components will be applied to IDegLira.

Based on the clear efficacy and reduction of important side effects, IDegLira has a favorable benefit-risk profile as an alternative to basal insulin intensification.

These benefit-risk conclusions are relevant regardless of the preceding antidiabetic medication. This includes patients who are insufficiently controlled on oral antidiabetic agents.

In clinical practice, the decision to initiate IDegLira, in a patient uncontrolled on OADs will be an individualized clinical decision taken by the physician and the patient.

In this patient population, IDegLira may be most appropriate for those who need ambitious

therapy to achieve their A1c targets.

To summarize, therefore, IDegLira's favorable benefit-risk profile has been demonstrated in our phase 3 program across a broad spectrum of people with diabetes, including those previously inadequately controlled on oral medications, basal insulin or GLP-1 receptor agonists.

To conclude, IDegLira will offer an important treatment option for patients who need to intensify glycemic control, whether they are naïve to injectable therapies or already on them. It demonstrated impressive efficacy in terms of glucose lowering even over basal insulin, which has long been the gold standard of glucose reduction.

All of the phase 3 trials met their primary endpoints and up to 80 percent of patients achieved their A1c target of less than 7 percent. And this efficacy was achieved in a once-daily injection that can be given at any time of the day.

IDegLira also mitigated important side effects of GLP-1 receptor agonists and basal

insulin that have prevented patients and healthcare professionals from maximizing the efficacy of these therapies.

IDegLira demonstrated efficacy and safety in a diverse diabetes population on varied background therapies. And its safety profile was consistent with the two FDA-approved IDegLira components.

We thank you for your time and attention and we look forward to answering your questions.

Clarifying Questions to Applicant

DR. SMITH: I'd like to thank the sponsor for those presentations. We now have some time for questions from the panel. And what I'm particularly looking for at this point is clarifying questions regarding the data.

We will have time this afternoon to ask questions that may be relevant to the discussion points and questions from the FDA. And also, if you'd be as focused as you could, we do have limited time.

Anyone with questions can signal me or Commander Bonner, and I'll make an effort to reach

everyone. If I don't do that this morning, we'll come back to you later in the day.

If you would, state your name at the time of your question as well. Ken?

DR. BURMAN: Ken Burman. Just two quick questions for the sponsor. Is my memory correct that, in the briefing book, the combination drug caused medullary thyroid tumors or medullary C-cell hyperplasia in two species of animals?

DR. GOUGH: I missed it. [inaudible - off mic].

DR. BURMAN: Sure. Is my recollection correct that in the briefing booklet, the combination drug caused C-cell hyperplasia and neoplasms in two species?

DR. GOUGH: That was not reported with IDegLira, no. That was previously reported with liraglutide.

DR. SMITH: I have a couple of questions. One was, recognizing that you have a dose cap on the device as it's designed, what is your thinking about how in practice and what your advice would be

in approaching patients who may be inadequately controlled when they reach the maximum dose?

DR. GOUGH: So I think it's important for me to point out that even those patients that got to maximum dose- -for example in 3697, 40 percent of the patients got to the maximum dose. But of those, 70 percent achieved their target A1c of less than 7 percent.

But for those that do get to the maximum dose, clearly, other alternative treatment options are available and should be considered. And this is a common problem that healthcare professionals find every day in managing type 2 diabetes.

But to specifically address your question as to what options might be available or what you might do in that situation, I'll call upon my clinical expert, Dr. Sorli, just go to through that.

DR. SORLI: I think, obviously, there will be patients who reach that dose cap and are not at goal. I think the clinical option at that point would be individual components.

Probably in that patient population, they're going to be very insulin resistant, so we're going to want to maximize the GLP-1 dose and then be able to titrate basal insulin.

Many of them will need very high dosages of basal insulin, so you'll almost have to do that combination and self-titrate the basal insulin.

DR. SMITH: So you're anticipating at that point they would cease using the device and just shift to purely the individual components. I'm just curious. It's really a practical clinical practice question to understand what we may encounter as people might use this device in practice.

DR. GOUGH: I didn't give Dr. Sorli an opportunity to answer that. From our point of view, we've clearly only investigated patients up to a dose of 50. But Dr. Sorli?

DR. SORLI: Yes, absolutely. Yes, we would come off the device and go to individual components. Yes.

DR. SMITH: Dr. Wilson?

DR. WILSON: Thanks very much. I think my question is also related to Dr. Smith's. So the sponsor slide CO-48, I'd like to understand a little bit better.

So the IDegLira group and the degludec are on 45 units and there's still a major difference. And I was wondering what would happen, trying to understand exactly what's happening with the dosing.

For instance, in the last third, from week 18 onto 26, if somebody was being dosed with degludec, you would think they would keep going and they would have ended up having more insulin, in fact. But were they supposed to get exactly the same amount? Maybe I don't understand the titration strategy. Is my question clear?

DR. GOUGH: Yes, very clear. So in Trial 3912, as with our other trials where we've compared IDegLira to basal insulin, they used exactly the same titration algorithm.

So if they were above target, they increased by a dose of 2. If they were below target, they

reduced their dose by a dose of 2. And this was based on three consecutive fasting blood glucose readings that were performed by the patient every day and adjustment was made twice a week.

As you can see in the top graph, the aim of this study was to achieve comparable insulin doses using the same algorithm and we achieved that. So you can see on a weekly basis, they were very similar, if not identical and certainly superimposable insulin values, insulin doses, such that at the end of trial, patients were also on exactly the same mean dose of insulin whether they were in IDegLira or insulin degludec.

This trial was specifically designed this way so that we could demonstrate the liraglutide contribution. And the difference in A1c that you're seeing is a result of the liraglutide contribution.

In both treatment arms, the patients could increase the insulin dose and indeed did so, but it was capped at a maximum of 50. And as you can see the mean doses, I previously mentioned, was 45. So

the difference between the A1c is the result of the liraglutide.

DR. SMITH: That's clear? You got your answer?

DR. WILSON: I got my answer, I think. I guess, in your different trials, you don't have what I was asking. You didn't do differential titrations. Could you have gotten there with an insulin product alone? And that ends up being some of the comparisons with glargine as well.

DR. GOUGH: I can talk to Trial 3952 where we had the same titration algorithm, but where we compared IDegLira to unrestricted insulin glargine, this was a treat-to-target study, and the insulin dose continued to increase in the insulin glargine group.

However, importantly, although the insulin dose increased, the fasting glucose values remain stable over the last 12-14 weeks of the trial so that the A1c value that we measured at the end of the trial was consistent with that period of stability.

I can just show you on this slide here, these are the self-monitored fasting glucose values for Trial 3952 where you can see similar titration values with respect to the insulin dose.

You can see that, with respect to the insulin glargine, the dose continued to go up throughout the period of the study. But it did so to achieve and maintain the same fasting targets as that which we saw with IDegLira.

DR. SMITH: Okay. Dr. Meisel, you had a question?

DR. MEISEL: I've got a couple of relatively quick clarifying questions. In a couple of the trials there on the metformin plus or minus pioglitazone or plus or minus sulfonylurea -- depending what they were on before the start of the trial, I presume- -did you do any subgroup analysis to see any differences for those who were or were not on, say, the pioglitazone?

DR. GOUGH: Yes. In Trial 3697, 80 percent of patients were on metformin and 20 percent of patients were on metformin and pioglitazone. And

if we look at our efficacy results, there was no difference between those patients that came in on the metformin or metformin and pioglitazone.

As you say, it was continued throughout the period of the trial. So no, there was no difference in clinical efficacy.

DR. MEISEL: Okay. Did you do any subgroup analysis based on the patient's BMI or weight? Did lower-weight patients respond differently than higher-weight patients either in terms of dose, outcomes, or whatever?

DR. GOUGH: We did do a subgroup analysis based on weight. And I can show you on this slide here, this is the change in A1c from baseline with IDegLira across the baseline BMI group. So this is BMI.

I can also show you it for weight but if we just look at BMI on this slide, for each of the trials, you can see we've broken weight down into quartiles so a BMI of less than 25 is the first band, then a BMI of 25-30, 30-35 and greater than 35.

You can see that each trial, irrespective of BMI, there were similar changes in A1c. So BMI -- and I can show you the same for weight -- had no impact on efficacy. IDegLira was equally effective across the BMI and weight range.

DR. MEISEL: And then if I may, a third question, are you considering these two agents to be additive or synergistic?

DR. GOUGH: We're unable to say whether they have -- how they're working. The important point is that both components are contributing to the reduction in A1c across the dose range.

But because our studies were treat-to-target studies, by the very nature of the design of the study, we cannot say how they're working in terms of an additive effect. We can say there's no evidence of a synergistic effect.

DR. MEISEL: Okay. And then one last question if I may. In your post-marketing reports in the briefing book, they refer to, I think, three medication errors overseas. Could you describe what those were?

DR. GOUGH: I can call upon Dr. Hobbs to take you through those, the data you're requesting.

DR. HOBBS: Actually, we've identified six medication errors from the UK where these occurred and there's no real pattern. There are some indication differences there in the UK so where a patient cannot be on another oral agent with Xultophy, for instance.

But I can certainly show you what we have collected in there here. I think you can see there's not any specific pattern. Patient was given both a GLP-1 agent along with Xultophy and recognized that immediately. Then they had a hypoglycemic reaction and came back. So there's very few in consideration of the number of countries where we've launched.

DR. SMITH: Dr. Everett?

DR. EVERETT: Thank you. So my question has to do with the sponsor slide 37 and specifically, I was surprised to see that, in the 26-week study in the IDegLira arm, there was 12 percent of patients that were withdrawn and as many as 18 percent in

the liraglutide arm.

So I have a couple of questions. The first is I don't have a lot of understanding looking at the reasons for withdrawal that were on the table here, what the withdrawal criteria are, because that seems to be where the majority of the patients are that category.

It's concerning to me and I should point out too that, not on this slide, but in the 3912 study, there was about 15, 16 percent of patients that were also not followed to the end of a relatively short study.

What are the reasons for the patients' withdrawals in this category, number one? And number two, can you help me understand what you did with their data in terms of the actual efficacy analysis and how that may have affected your change in hemoglobin A1c or your A1c endpoint?

DR. GOUGH: Yes. With respect to the first part of your question and the discontinuations by our pre-specified withdrawal criteria for Trial 3697, this gives you a breakdown of the

reasons.

You can see these include that it was the patient's own will, the patient's own decision, decided to withdraw. The second category was they were noncompliant and/or a safety concern.

The third was continuous high self-monitored plasma glucose values and we had specific criteria for those with different levels of blood glucose at different time points during the study, reflecting the titration process.

Whether they were being prescribed any other medications that could be interfering with treatment, there was pregnancy and acute pancreatitis. So that's a breakdown of the data that we have with respect to the pre-specified withdrawal criteria.

I'm sorry, the second part to your question?

DR. EVERETT: So what did you do with those patients in the analysis, the efficacy analysis?

DR. GOUGH: So I can call upon my statistician, Kamilla Begtrup, to tell you how we handled missing data.

DR. BEGTRUP: Kamilla Begtrup, principal statistician. So we did not collect any further observations from the patients when they withdrew from treatment. So we did not invite them in for the week 26 assessment. So in the analysis, we imputed their missing values by the LOCF as the primary analysis.

You can see here, we then did a number of sensitivity analyses to evaluate the impact of doing the LOCF, which has its limitations. So here, you see the results of the sensitivity analysis in Trial 3697, the comparison to degludec on the left and liraglutide on the right.

You have the primary analysis based on LOCF in the top row. And below, you have the results from the sensitivity analysis, which shows a very consistent result regardless of which method we have used to impute the missing data.

DR. EVERETT: So if the patient was enrolled and randomized and then did not have a single follow-up hemoglobin A1c value but received presumably one dose of the medication, that

baseline A1c value was their outcome which carried forward throughout the --

DR. BEGTRUP: Yes. The baseline was carried forward.

DR. EVERETT: -- regardless of the treatment arm.

DR. BEGTRUP: Yes.

DR. EVERETT: How certain are you that none of these patients discontinued and then went on to have a serious adverse event potentially related to treatment such as a cardiovascular event?

DR. GOUGH: So I can call upon Dr. Hobbs to take you through that, but I'm not aware that any of those patients did that. But I will ask Dr. Hobbs to comment.

DR. HOBBS: Well, we certainly followed the patients for safety reporting up to 7 days post-trial, wherever that would be, either completion of the trial or withdrawal.

As to how certain, I mean, obviously, it would be spontaneous reporting at that point which we did collect a few, mostly neoplasms and not any

CV after that point.

DR. SMITH: Dr. Neaton?

DR. NEATON: Thank you. I have a couple of questions and perhaps just a follow-up based upon Dr. Everett's question. The theme is kind of the number 42.

So on page 42 of your briefing document, you referred to a titration committee. I'd be curious to know exactly what this committee did. You mentioned that they made decisions blinded and talked to sites. But three of your studies are open label.

So can you say a little bit more about what the role of this committee was and potentially how there is any possibility of introducing bias here in terms of the how the arms were treated in this trial?

DR. GOUGH: So the aim of establishing the titration committee was based on practice of insulin treat-to-target studies. So it's an important requirement when conducting studies like this that both arms are treated equally and

effectively so that you have comparable A1c's at the end of the studies so you can compare the secondary parameters.

So to ensure this, we had a titration committee and we had a process whereby it was a centralized Novo Nordisk independent titration committee that was not involved in the clinical trial. And they also had nurses who were based in the U.S. who also reviewed, on a regular basis, how the titration process was going.

As I said, the aim was to ensure a balance and equal titration in both treatment arms. The nurses would review the blood sugar readings that the patients were collecting as they're being transferred from the diary to the electronic data capturing system.

They would review the mean glucose values. They would see if the titration process had been adhered to and, if not, would contact the center and see if there was a reason for that. With respect to --

DR. NEATON: Did this lead to then

discussions with sites about individual patients that were apparently not adherent?

DR. GOUGH: Yes, by contact. However, the final decision to titrate any patient was always based on the judgment and the decision of the principal investigator. So this committee did not override any of the decisions taken by the principal investigator.

DR. NEATON: About how often did this occur in the trial?

DR. GOUGH: With respect to the review of diaries and blood glucose readings, that was done on a regular basis, on a weekly basis.

DR. NEATON: Okay. Let's go to another question. Let's look at slide 42, staying on the 42 theme here. So I mean, the statement here that regardless of the dose, there's efficacy of the combination, I found a little kind of difficult to take.

I mean these groups are no longer comparable, the way you've defined them. So because you're stratifying them on the dose of

insulin, it's something that was determined post-randomization. It's a reasonable question, but I guess I question whether this is the appropriate analysis.

So do you have any information? For example, what are the baseline characteristics of the people who required a higher dose of insulin and how they might differ from people that were able to be maintained on a lower dose of insulin?

DR. GOUGH: We have looked at the baseline characteristics of patients that are on the higher and lower doses. We've also performed other analyses to look at the contribution of liraglutide to these low doses.

But if I, first of all, show you the baseline characteristics of those patients, we've taken a cut point here of 32. And the reason we've taken a cut point of 32 is that's equivalent to the minimum maintenance dose of liraglutide when used alone. So that's the maintenance dose of 1.2.

So you can see here, for each of the three clinical trials where we have an insulin

comparator, you can see the characteristics of patients who are on less than 32 and the characteristics of patients who are on more than 32.

If you look down each of the columns, there are some minor differences in terms of the absolute values, but there's nothing there that would enable us to predict which patients would require a higher or a lower dose.

DR. NEATON: I guess I would say that there's more than minor differences there. I mean, the weight differences seem pretty large, as do the differences in gender.

Have you considered, for example, using this information to develop some type of prognostic kind of index for who might require a higher dose and then using that to stratify the two treatment arms? I mean that, at least, is protected by randomization.

DR. GOUGH: We do know that females are more sensitive to IDegLira and we do know that patients with a lower BMI and body weight, lower weights and

BMI, does increase -- those patients are more sensitive. But it's difficult for us to categorize patients in advance based on how they're likely to respond.

DR. NEATON: Okay. Kind of two other quick questions about --

DR. SMITH: Very quick because we need to start up our --

DR. NEATON: The cardiovascular outcome trials, in the LEADER trial, for example, you said it's in the background of standard of care. Is there a large fraction of the people that are taking insulin?

DR. GOUGH: I can call upon Dr. Hobbs to take you through information that he currently has on LEADER.

DR. HOBBS: It's a very brief answer in terms of we really don't have the opportunity to see the full data from the LEADER trial.

DR. NEATON: I know.

DR. HOBBS: And so I would like to avoid spending substantial time probing data in the

LEADER trial --

DR. NEATON: My question is simple because I'm trying to understand what is the potential cardiovascular safety data you're going to have for the combination.

DR. HOBBS: What I can tell you is the baseline had around 40 percent that entered on insulin. So that's pretty much the short answer, but that's what we can share at this point.

DR. NEATON: I'll pass on the next question.

DR. SMITH: Okay. I know there are a few panel members who I didn't yet get to and we will come back to you later today. And if I fail to do that, please flag me down and make sure I do.

We're going to now take a short break. 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.

We're going to resume, let's say, at 10:27. All right. I know that's a sharp number but I've slightly shortened the break and I want to make

sure we have as much time for discussion as possible. So about 28, 27 past the hour, we'll start.

(Whereupon, at 10:14 a.m., a recess was taken.)

DR. SMITH: I'd like to call the meeting to order again. We're going to proceed with the FDA presentations. I guess Dr. Condarco is going to lead this off.

FDA Presentation - Tania Condarco

DR. CONDARCO: All right. Good morning. My name is Tania Condarco. I am clinical reviewer in the Division of Metabolism and Endocrinology Products. I would like to thank the committee for being here today.

Today, we will discuss the findings in the new drug application for insulin degludec and liraglutide. In my presentation, I will provide an overview of the product and its development, after which I will introduce the phase 3 trial designs.

After this, I will turn the presentation over to Anna Kettermann, the FDA's statistical

reviewer, who will present the efficacy overview. Then I will return to discuss the clinical interpretation and relevance of the phase 3 trials and provide an overview of safety findings before concluding.

The following abbreviations will be used throughout the presentation. I will refer to the combination product of insulin degludec and liraglutide as IDegLira.

Let's start the discussing the background and product overview. There are 12 classes of drugs approved in the United States for the treatment of type 2 diabetes.

One of these classes is glucagon-like 1 receptor agonists or GLP-1 for short. These are administered by subcutaneous injection and there are currently five approved options for patients. More recently approved products can be administered once weekly.

Basal insulins that can be administered via subcutaneous injection once a day are shown here. Insulin degludec and liraglutide, which are

approved products, are the components of the fixed-combination drug, IDegLira.

Insulin degludec was approved in 2015 under the trade name Tresiba. Insulin degludec is a long-acting insulin analogue indicated to improve glycemic control in adults with diabetes mellitus. The recommended dosage is once daily at any time a day.

In clinical use, the dose of insulin degludec is individualized based on patient's metabolic needs, glucose monitoring results, and glycemic goals.

Liraglutide was approved with a trade name Victoza in 2010 at a maximum dose of 1.8 milligrams as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Victoza is initiated at 0.6 milligrams per day for one week. This dose is the starting dose intended to reduce gastrointestinal symptoms during initial dosing and is not an approved dose for glycemic control.

After one week, the dose should be increased to 1.2 milligrams. If the 1.2-milligram dose does not result in acceptable glycemic control, the dose can be increased to 1.8 milligrams.

IDegLira is a fixed-ratio combination product of insulin degludec and liraglutide. The liraglutide and insulin degludec drug substances for the IDegLira formulation are identical to the drug substances used for the Victoza and Tresiba products.

For every unit of degludec, there is 0.036 milligrams of liraglutide. For example, a dose of 32 of IDegLira would administer both 32 units of insulin degludec and 1.16 milligrams of liraglutide. I specifically emphasize this dose since I will refer to it later in my talk.

The proposed pen device allows for dose range of 1 unit of degludec and 0.036 milligrams of liraglutide to a maximum dose of 50 units of degludec and 1.8 milligrams of liraglutide.

Because of the product presentation of IDegLira as a fixed-ratio solution, the individual

components cannot be dosed individually. For example, a patient cannot reduce the insulin dose and keep the liraglutide dose the same. This contrasts with the way Victoza and basal insulin are used in clinical practice as two separate products.

The potential clinical implications of this approach are illustrated by the following hypothetical examples. For one, a patient using Victoza needing additional glycemic control would have to reduce the liraglutide dose to initiate IDegLira therapy.

Another example is a patient using IDegLira and experiencing hypoglycemia from the IDeg component. To reduce the insulin dose, the liraglutide dose would also have to be reduced.

Because IDegLira is a combination of two drugs, the FDA recommended that the primary objective of the phase 3 program was to demonstrate that each component contributed to the claimed effect of glycemic control as specified in the regulation 21 CFR 300.50, as shown here.

There was no precedent to apply the combination rule to a product that combines a titratable drug with a fixed-dose drug. And there was a question of what the best trial design would be to demonstrate contribution of the fixed-dose liraglutide component to the glycemic effect because the comparator, insulin degludec, would not have a maximal dose.

In other words, there was concern it would be difficult to show statistical superiority of IDegLira versus IDeg because IDegLira has a maximum insulin dose of 50 units, whereas IDeg does not have the same limit.

The division stated that, for the purposes of a trial designed to satisfy the regulatory requirement for combination drugs, it would be acceptable to limit the maximal degludec dose to 50 units, in other words, cap the dose of IDeg to evaluate the superiority of IDegLira versus IDeg and establish the contribution of liraglutide to the claimed effect.

The trial would be designed to meet a

regulatory requirement. However, there was still residual uncertainty about how this type of data would be generalizable to clinical practice.

Now, I will discuss the phase 3 trial designs. The IDegLira program had five phase 3 trials. Two of the IDegLira trials included subjects with type 2 diabetes mellitus never previously treated with either a basal insulin or a GLP-1 agonist. In other words, they were starting two new drugs at once.

The first of these was Trial 3697, the factorial study. Trial 3697 was an open-label trial in which subjects, failing therapy with metformin, with or without pioglitazone, were randomized to IDegLira, liraglutide or IDeg while continuing their pre-trial antidiabetic therapies.

This trial evaluated the hemoglobin A1c reduction with IDegLira relative to liraglutide, thereby testing the contribution of the IDeg component of IDegLira to the claimed effect. Of note, in this trial, there was a third arm that randomized patients to IDeg with no dose cap.

In this trial, the mean age was 55 years; BMI was 31; diabetes duration was 7 years; baseline hemoglobin A1c was 8.3 percent; and 83 percent of patients were on metformin alone at screening while about 17 percent of patients were taking metformin and pioglitazone.

The second trial in subjects not previously treated with GLP-1 or insulin was Trial 3951. This was a double-blinded trial in which subjects failing therapy with sulfonylurea, with or without metformin, were randomized to IDegLira or placebo while continuing their pre-trial antidiabetic therapies.

In this trial, the mean age was 60 years; BMI was 32; diabetes duration was 9 years; baseline hemoglobin A1c was 7.9 percent; and 11 percent of patients were on sulfonylurea alone at screening. Virtually all the patients were taking sulfonylurea and metformin. This trial was not required by the FDA.

Two trials were in previous basal insulin users. The first of these was Trial 3912.

Trial 3912 was a double-blinded trial in which subjects failing therapy with basal insulin at doses of 20-40 units plus metformin with or without sulfonylurea and with or without a glinide were randomized to IDegLira or IDeg.

Subject randomized were inadequately controlled and some of these were randomized to a version of their pre-trial treatment. This trial evaluated the hemoglobin A1c reduction with IDegLira relative to IDeg capped at a maximum dose of 50 units, thereby testing the contribution of the liraglutide component of IDegLira to the claimed effect.

Pre-trial, most subjects were taking metformin with or without sulfonylurea or glinide. At randomization, all non-metformin therapy was discontinued. This aspect of trial design is unique to Trial 3912. In all other trials, background therapy was continued at pre-trial doses.

In this trial, the mean age was 57 years; BMI was 34; diabetes duration was 11 years;

baseline hemoglobin A1c was 8.8 percent; and the mean basal insulin dose was 29 units.

The second trial in previous basal insulin users was Trial 3952. This trial was an open label trial in which subjects failing therapy with insulin glargine and metformin were randomized to IDegLira or to continue insulin glargine while continuing metformin.

Pre-trial, most subjects were taking metformin. In this trial, the mean age was 59 years; BMI was 32; diabetes duration was 12 years; baseline hemoglobin A1c was 8.3 percent; and the mean insulin dose was 32 units.

One trial in the IDegLira program was conducted in previous GLP-1 analogue users. Trial 3851 was an open label trial in which subjects failing therapy with liraglutide administered once daily or exenatide administered twice a daily at their maximally effective doses with metformin, with or without pioglitazone, and with or without sulfonylurea were randomized to IDegLira or to continue their pre-trial GLP-1 and

oral antidiabetic drugs.

In this trial, the mean age was 58 years; BMI was 33; diabetes duration was 10 years; baseline hemoglobin A1c was 7.8 percent. At screening, all patients were on metformin, about 4 percent were on pioglitazone, about 23 percent were on sulfonylurea.

There are potential clinically important uses of IDegLira that were interesting clinical questions but were not required to be studied. One is comparing the effectiveness of IDegLira versus independent injections of degludec and liraglutide 1.8 milligrams.

A study with this design could potentially inform the selection of specific therapy. Another is converting subjects using a long-acting GLP-1 and a basal insulin independently to IDegLira. This would test whether IDegLira is an option for patients already using both therapies.

Now, I am going to discuss the dosing of IDegLira and insulin comparators, which is important for interpreting efficacy results.

Adjustments of IDegLira and comparator insulin or placebo should have been performed twice weekly based on fasting self-monitored plasma glucose levels, referred to as SMPG. The specific SMPG goals will be discussed later in the presentation.

The dose change algorithm, shown in the table -- in all studies, the average SMPG value was below the pre-specified goal. A dose decrease of 2 for IDegLira and 2 units for the comparator insulin was recommended. If at goal, there was no change.

If the SMPG average was above the pre-specified goal, a dose increase of 2 for IDegLira and 2 units for the comparator insulin was recommended. Because titration occurred twice weekly, the most a dose could increase in a given week was 4 for IDegLira or 4 units for basal insulin.

With that, I have completed the product overview in the phase 3 trial design section of this talk. Anna Kettermann will now present the statistical overview of efficacy.

FDA Presentation - Anna Kettermann

MS. KETTERMANN: Good morning. My name is Anna Kettermann. I am a statistician in the Office of Biostatistics in CDER. Today, I'm going to present the FDA statistical assessment of efficacy.

I will begin with a discussion of primary and secondary efficacy results. Then, I will characterize the missing data and discuss its impact on primary outcome.

I will discuss a major limitation in trial design, specifically the titration regimen and its impact on the external validity of the results. I will wrap up with conclusions.

The primary objective of the set of five trials was to determine the superiority of IDegLira in reduction of HbA1c from baseline to week 26 against various comparators.

I will present treatment differences based on mixed-effect model repeated measure approach with covariates baseline HbA1c, visited country, and background medications, among others.

The impact of missing data was evaluated

using multiple imputations and also through tipping-point analysis. A major limitation of the data collection in IDegLira program was the absence of retrieved dropout, which limits the choices for sensitivity analysis and affects the interpretation of the results.

Results from the MMRM analysis are shown here for each of the five studies. Let me walk you through the graph. Study numbers are shown on the X-axis. The Y-axis shows the treatment differences in HbA1c between IDegLira and comparator.

The graph shows the estimates and 95 percent confidence intervals of difference between 26 weeks HbA1c levels in comparator and IDegLira arm. Each symbol represents a separate comparator, and each color represents a different study. The blue circle and blue triangle show the estimated treatment differences between IDegLira and comparators, IDegludec and lira in study 3697.

The red triangle shows the estimated difference between IDegLira and GLP-1 in study 3851. The green circle shows the difference

between IDegLira and IDegludec capped at a dose of 50 units in study 3912.

The purple square shows the difference between IDegLira and placebo, study 3951. And the black diamond is for the differences between IDegLira and insulin glargine in study 3952.

Negative values indicate larger reduction of HbA1c for IDegLira arm than for the comparator arm. The graph illustrates that all differences between final outcomes were below zero and therefore show superiority.

I will now shift focus to the important issue of missing data. Missing data are important because not only they can affect the integrity of randomization, but also can introduce bias.

There are likely differences in the adherence to therapy between subjects who have HbA1c measurements and those who do not have HbA1c measurements.

Therefore, the HbA1c values for those subjects with missing data may not be well represented by HbA1c measurements of subjects in

the same treatment arm. I will discuss this in the next two slides.

This slide shows the amount of missing endpoint data for each treatment group in each study. Across studies and all treatment groups, the missing data range from 5 to 25 percent. The missing data range were fairly similar across treatment groups in studies 3697 and 3912.

In study 3851, the dropout rate for GLP-1 arm was notably higher than for IDegLira arm and the majority of dropouts were due to gastrointestinal adverse events. More detail about dropouts due to adverse events will be discussed by Dr. Condarco in her safety presentation.

In study 3952, the missing data rates were at 10 and 5 percent respectively for IDegLira and insulin glargine. The low dropout rate in the glargine arm of the Trial 3952 is notable and may be due to the fact that most subjects were on glargine at the time of enrollment.

The largest dropout was one-quarter of all placebo subjects in study 3951. In this arm, the

majority of reason for dropout were treatment failure.

The impact of missing data was assessed using multiple imputation and tipping-point analysis. Two approaches to multiple imputation yielded similar results favoring IDegLira against all comparators.

Tipping point analysis indicated superiority except under implausible circumstances. In other words, in order not to be able to conclude superiority, we would need very unlikely conditions.

There were two secondary objectives for the IDegLira program, change in body weight and reduction in number of treatment-emergent confirmed hypoglycemia cases. The latter will be discussed by Dr. Condarco as a safety endpoint.

In the IDegLira program, change in body weight was investigated as a secondary endpoint. As seen on this graph on the left, in study 3697, body weight changes favored IDegLira over IDegludec.

At the same time, body weight changes were more favorable in lira when compared to IDegLira. In the middle graph, in study 3851, body weight changes favored GLP-1 over IDegLira. On the right, in study 3951, body weight changes favored placebo over IDegLira.

Although the treatment differences were statistically significant, they were also small. When comparing IDegLira to insulin comparator, the weight differences were between 2.4-3.3 kilos in favor of IDegLira. The clinical relevance of changes in body weight will be discussed by Dr. Condarco.

Three limitation of body weight analysis are: Only one study had 52-week data; the last 26 were extension and not part of primary efficacy analysis.

For drug intended for weight management, efficacy and safety are evaluated in 52-week trials. The study did not continue for subjects who prematurely discontinued treatment. And the change in body weight was not consistent among the

different trials. This is most likely due to differences in patient population and comparators.

Now, we have completed our discussion on trials objectives. Next, I will discuss an important limitation in trial design. Specifically, I will discuss the titration regimen and its impact on study results.

For trials that had an insulin comparator arm, there were two approaches to insulin doses. One is a capped approach, which is limited the number of dose of insulin degludec to 50 units.

This design was intended to test for superiority of IDegLira versus IDegludec. But this is not how insulin is used in clinical practice. The other was allowing titration of insulin to reach glycemic targets.

For the purposes of this presentation, this approach is called an uncapped approach, and this was used in two trials, 3697, the three-arm trial, and Trial 3952, which studied IDegLira versus insulin glargine.

I will provide my methodology for

understanding the behavior of dose stabilization in the next slide.

Dose is considered to be stable when the investigator stopped increasing the dose. Time to dose stabilization is time to when the dose increase has stopped. As a reminder, dose changes were based on self-measured plasma glucose. I will discuss the capped approach in the next slide.

All treatment-specific insulin dose values in my presentation are estimates from the MMRM model adjusted for covariates, including baseline HbA1c and all other covariates that were pre-specified in the primary analysis.

Dose stabilization in capped titration approach is listed on this slide in Trial 3912. The graph on the left shows average insulin doses taken by subjects over 26 weeks.

Once the maximum dose of 50 units was reached, the dose was not allowed to increase further. Note that the curve for the subjects on IDegludec in blue matches the curve for subjects in IDegLira in red, suggesting that insulin dose was

similar between the two arms over time.

The curve on the right shows the percentage of subjects who completed their titration period by study week. The horizontal dashed line shows the time point where 50 percent of subjects reached stabilization.

This time point occurs around week 10 for IDegludec and week 11 for IDegLira. Therefore, titration goals set for the trial appear to have been reached early and were similar between arms.

As I will show you next, this did not appear to be the case in the uncapped trial, 3697. The graph on the left shows average insulin doses taken by subjects over first 26 weeks in the uncapped trial, 3697.

The red curve representing IDegLira becomes flat after approximately halfway through the 26-week period, signifying the end of titration period. In contrast, the blue curve showing IDegludec continues to rise, indicating that dose stabilization was not reached by most subjects by 26 weeks.

Again, the curve on the right shows cumulative percentage of subjects who completed their titration period as a function of study week. As a reminder, the titration algorithm was the same in all trials.

Fifty percent of subjects in IDegLira arm reached stabilization around week 16, marked by a vertical red arrow. However, only 25 percent of subjects in IDegludec arm reached their stable dose by week 16.

In the end of the trial, half of the subjects in IDegludec arm reached dose stabilization. Therefore, half of the subjects had final HbA1c reading at week 26 that was still evolving and the comparison of 26-week HbA1c might not be reflective of comparison at longer duration.

Going back to the blood glucose changes in Studies 3912 and 3697, this slide shows centrally measured fasting plasma glucose by study week for Trial 3912 on the left and 3697 on the right.

IDegludec is in blue and IDegLira is in red. In the graph on the left, showing the capped dosed

trial, 3912, FPG levels stabilize in both arms around week 12 and remain parallel for the duration of the trial. This pattern is consistent with previously presented dose stabilization curves.

In the graph on the right, again, IDegludec is in blue, IDegLira is in red, and the liraglutide alone arm is shown in green. Focusing on the IDegludec and IDegLira arms, it is clear that FPG for subjects on IDegludec was continuously dropping during the entire trial and approximated FPG for subjects on IDegLira only towards the end of the trial.

In conclusion, the primary endpoint was met within the five trials as conducted. The missing data do not affect the conclusion of superiority of IDegLira on 26-week HbA1c.

Due to the insulin titration in insulin comparator trials, there is a concern that the treatment difference overestimates what would be seen in clinical practice.

Body weight changes were consistent with no effects of insulin degludec and liraglutide.

Statistically, weight changes were different between IDegLira and comparators but those changes were small.

Overall, subjects on IDegLira gained less weight than subjects on insulin. In contrast, weight reduction among subjects on IDegLira was significantly smaller than weight reduction among subject on GLP-1 and subjects on placebo.

Additionally, the interpretation of the comparisons on body weight change are also limited by the study duration and the lack of retrieved dropouts.

Thank you.

FDA Presentation - Tania Condarco

DR. CONDARCO: Now, I will discuss FDA's view of the clinical relevance of the efficacy findings. As was just discussed in the statistical presentation, efficacy results showed that IDegLira was superior to continuing pre-trial GLP-1 therapy in patients failing GLP-1 with both arms on a background of oral antidiabetic drugs.

IDegLira was also superior to placebo in

patients on a background of sulfonylurea and metformin. In Trial 3697, IDegLira was superior to treatment with liraglutide, both on a background of oral antidiabetic drugs. The comparison of IDegLira versus uncapped IDeg will be discussed in a subsequent slide.

The results for the insulin dose-capped trial, 3912, showed superiority of IDegLira versus IDeg capped at 50 units thereby demonstrating the contribution to glycemic control from the liraglutide component.

We note again that the dosing cap limits generalizability to clinical practice where patients would not be limited to 50 units.

Statistical superiority was also demonstrated for IDegLira versus IDeg in Trial 3697 and over glargine in Trial 3952. However, the external validity of the trials is unclear because of issues related to dosing of the insulin comparator.

I will walk you through these issues in the next part of the presentation. To facilitate this

discussion, I will first briefly explain a few concepts related to hemoglobin A1c as an efficacy endpoint in insulin trials.

Hemoglobin A1c measures a time-weighted average of glucose concentrations over a period of 12-16 weeks in an individual subject. Therefore, it would take 12 to 16 weeks for a maximal drug effect to be fully reflected in the hemoglobin A1c measurement.

To fairly interpret the effect of a drug on hemoglobin A1c, the maximally effective dose of a drug has to be reached at least 12 to 16 weeks before the final hemoglobin A1c measurement.

For a fixed-dose drug, this is not an issue. But for a titratable drug, there can be challenges, as I will discuss in the next few slides.

In a typical 26-week glycemic control trial for a fixed single-dose product administered at a maximally effective dose, the patient starts at a specific dose at week zero and continues at the same dose to the end of the trial without change.

In this case, the 26-week hemoglobin A1c

measurement would fully reflect the glycemic effect of the administered dose of the drug because the dose is stable for the 12 weeks prior to measurement.

However, for a titratable drug, there are multiple factors that affect its dosing. To illustrate these factors, I will use the analogy of a race.

The first factor is where you start. In a trial, this would be equivalent to the starting dose of a product. In the context of insulin trials, the lower your dose, the longer it will take you to reach the effective dose.

The second factor is how fast you go. In the context of a drug trial, this would be equivalent to weekly dose increases, which is dependent on the magnitude and frequency of titrations.

The third factor is how far away is the finish line. In the context of drug trials, this would be equivalent to the SMPG goal. The lower the target, the longer it will take you to reach

the goal.

Also, the duration of the trial matters. All of these factors will be more important in a shorter-length trial.

As stated previously, we need a stable dose of at least 12 weeks so that hemoglobin A1c will fully reflect the effect of the drug for a titratable drug in a hypothetical 26-week trial, dose increases for the first 12 weeks, and then reaches a stable dose by week 12.

The figure on the right shows a titratable drug that does not reach a stable dose. The glycemic lowering achieved during continued titration after week 12 is represented by the yellow-shaded area.

This glycemic lowering effect would not be fully reflected in the 26-week hemoglobin A1c. In this later situation, the trial results can be challenging to interpret. As I will discuss, this situation occurred in the IDegLira program.

As noted by the FDA statistician, there were challenges in interpreting the hemoglobin A1c

results in the insulin comparator trials because of imbalances in time to dose stabilization in uncapped studies. As a reminder, the FDA statistical reviewer defined time to dose stabilization as the time when the dose stopped increasing.

This imbalance resulted from three aspects of the dosing regimen. First, was use of the same titration algorithm for one drug versus a two-drug product; second was the conservative rate of titration; and third was the low SMPG goals relative to usual clinical practice.

I will now go through each of the three listed factors and how each applies to the IDegLira program. The use of the same titration algorithm for one drug versus a two-drug product resulted in differences in time to dose stabilization.

In the comparator insulin trials, at every visit where titration occurred, IDegLira would go up by 2 units of degludec and 0.072 milligrams of liraglutide while the comparator insulin would only increase by 2 units.

Because IDegLira contains two glucose lowering drugs whose individual components lower blood glucose, the use of the same titration algorithm and the same titration schedule in both IDegLira and the comparator insulin over time would be expected to result in a faster glycemic lowering for IDegLira than for the comparator insulin. This would be expected to put the insulin arm at a disadvantage.

The conservative rate of titration also affected the interpretability of trial results. In clinical practice titration usually aims to increase the dose proportionally to the level of hyperglycemia so that, for blood glucose levels slightly above goal, there may be a lower increase of insulin dose than if blood glucose levels are much higher than goal. In this program, there was only one option for dose increase of 2 units up.

In comparison, the titration algorithm in the original development program for insulin degludec increase doses more quickly. By comparing the IDegLira titration, on the left, to the insulin

degludec titration algorithm used in the type 2 diabetes phase 3 trials, it appears that the magnitude and the limited number of titration steps in the IDegLira algorithm was relatively conservative.

Another titration issue was related to the low glycemic goals. In general, the IDegLira titration goals shown in this table by trial were relatively low.

Lower titration goals can contribute to a longer time to reach dose stabilization. And in the race analogy, it's like having to run a longer distance.

I will now discuss how titration issues influence the interpretation of Trial 3952, which studied IDegLira versus insulin glargine with no dose cap.

The figure on the left shows insulin dose by study week and the figure on the right shows the proportion of subjects reaching glycemic goals by week of study. IDegLira is in red and glargine is in purple.

The first point I'd like to make is that early in the trial, the slopes of the two curves are similar as shown in the insulin dose by week graph on the left, which is reflective of the similar dosing algorithm.

In the graph on the right that shows the proportion of subjects that achieved SMPG titration targets by week of study, you can see that early in the trial, there was a higher proportion of IDegLira subjects reaching goals.

However, because more patients were reaching glycemic goals in the IDegLira arm, the slope begins to flatten out in this arm, but the glargine subjects continued to go up on their dose and do not seem to reach a stable dose by week 26.

In the graph on the right, you can see the proportion of subjects reaching goals in the glargine arm is still increasing towards the end of the trial.

Half of the patients reached dose stabilization at week 12 for IDegLira and week 19 for glargine, meaning that half of the patients in

the glargine arm were still titrating within 7 weeks of study end.

These exploratory analyses suggest that hemoglobin A1c measured at 26 weeks may not be reflective of a period of glycemic stability for the glargine arm, making comparisons between arms challenging.

A similar pattern was seen in Trial 3697, the three-arm study. Since the discussion is regarding titration, data from the liraglutide arm were omitted for simplicity.

Again, the figure on the left shows insulin dose by study week and the figure on the right shows the proportion of subjects reaching glycemic goals by week of study. IDegLira is in red and IDeg is in blue.

Early in the trial, the slopes of the two curves are similar which is reflective of similar dosing algorithm and a higher proportion of subjects in the IDegLira arm are reaching glycemic goals.

However, because more patients were reaching

glycemic goals in the IDegLira arm, the slope begins to flatten out in this arm. But the IDeg subjects continue to go up on their dose and do not seem to reach a stable dose by week 26.

The graph on the right shows the proportion of subjects reaching goals in the IDeg arm is still increasing towards the end of the trial.

As discussed by the FDA statistician, half of the patients reached dose stabilization around week 15-16 for IDegLira and week 26 for IDeg. Overall, these exploratory analyses suggest that in the IDeg arm, the hemoglobin A1c may not be reflective of a period of glycemic stability and again making comparisons between arms challenging.

To summarize, stable hemoglobin A1c is needed for a fair between-arm comparison. In the uncapped trials, aspects of the dosing regimen did not result in a stable hemoglobin A1c by week 26 because the insulin comparator was still being titrated for many patients after week 12.

While statistical superiority was demonstrated, the external validity of these

results is unclear. In other words, it is uncertain if the IDegLira would be superior to insulin alone if the insulin comparator would have been fully titrated by week 26.

In regards to generalizability of these results to clinical practice, it can be concluded that the IDegLira development program demonstrated contribution to claimed effect for both components.

However, the trial design of the dose capped trial and the dosing concerns of the non-capped trials may limit the generalizability of the program results to clinical practice.

Conclusions over the contribution to claimed effect were based on the overall effect of IDegLira and not based on consideration of a minimum effective dose of liraglutide.

Now, I will shift my focus to discuss the dosing of the liraglutide component of IDegLira. In the Victoza label, 0.6 milligrams is the recommended starting dose. The minimum approved effective dose for glycemic control is 1.2 milligrams.

In pre-submission correspondence, the FDA expressed concern that subjects receiving less than the minimum clinically effective dose of IDegLira may not derive glucose-lowering benefit from the liraglutide component of IDegLira but may be exposed to risks associated with liraglutide use.

In order to understand the extent to which patients were taking less than 0.6 milligrams and 1.2 milligrams of liraglutide at the end of 26 weeks, we looked at the proportion of subjects in each trial on IDegLira who were using less than or equal to 16 of IDegLira, which would be equivalent to a dose of less than or equal to 0.58 milligrams of liraglutide. This is shown on the left, and subjects who were using less than or equal to 32 of IDegLira which would be equivalent to a dose less than or equal to 1.16 milligrams of liraglutide shown on the right.

The first three rows in these tables show the data from the phase 3 trials that enrolled previous insulin or GLP-1 users. Few of these subjects had doses less than 0.6 milligrams of

liraglutide, as shown on the left table, and ranged for 10 to 22 percent of subjects when looking at doses less than 1.2 milligrams of liraglutide, as shown on the right table.

Overall, it appears that the majority of subjects were taking at least 1.2 milligrams of liraglutide at the end of 26 weeks in this population.

On the other hand, in the trials of subjects not previously using insulin or GLP-1, overall, there were higher proportions with doses below these thresholds.

More than a quarter of subjects in the placebo-controlled trial, Trial 3951, received a liraglutide dose less than 0.6 milligrams. To remind you, Trial 3951 was a double-blinded, placebo-controlled trial in which insulin-naïve subjects were taking sulfonylurea and metformin and randomized to IDegLira or placebo.

Although factors such as the extent of disease and concomitant medications may have affected why patients in this trial reached these

low doses, a trial element that may have also contributed was the relatively more liberal titration goals with a target up to 108 milligrams per deciliter in this trial.

I will now discuss the safety findings of the IDegLira program. Because the safety profile of the individual components has been well characterized in the Victoza and Tresiba programs and Victoza's labeled for use with basal insulin, the safety program objectives of the IDegLira program were to evaluate for any new risks that may result from the combination.

The label safety issues for insulin degludec and liraglutide are shown. Safety issues for insulin degludec include hypoglycemia and weight gain. Safety issues for liraglutide include gastrointestinal adverse events, pancreatitis, thyroid neoplasms and increases in heart rate.

Both insulin degludec and liraglutide are labeled for immunogenicity and injection site reactions. IDegLira would be expected to carry both sets of risks.

Data from all five phase 3 trials were pooled for the evaluation of safety and four treatment groups were considered for safety comparisons.

The IDegLira group included IDegLira arm from all five completed trials. The basal insulin group included the combined data for the IDeg arm of Trial 3697 including the extension, 3912, and the IGlar arm of Trial 3952.

The GLP-1 group included the combined data for the liraglutide arm of Trial 3697 and the liraglutide exenatide arm of Trial 3851. Finally, the placebo group included the placebo arm of Trial 3951. Recall that these patients were also on a background of sulfonylurea therapy.

The baseline characteristics of the IDegLira population are shown here. The take-home here is that overall, the population was reflective of the type 2 diabetes population studied in glycemic control trials used for product registration.

Most of the patients were between the ages of 18-65 years of age. The majority of patients

were non-Hispanic white, one-third came from the U.S., 64 percent had diabetes for less than 10 years, most patients were obese, and most patients had normal to mild impairment of renal function. These characteristics were similar across the arms, so data only from the IDegLira arm is shown.

This slide shows the major safety findings of the phase 3 IDegLira program. There were a total of 4 deaths reported in the completed phase 3 trials, 3 in the IDegLira arm and 1 in the insulin glargine arm. 0.2 percent of the patients died in the IDegLira group and less than 0.1 percent in the basal insulin group.

The majority of deaths were due to cardiovascular causes and the clinical narratives did not suggest the cause of death as a result of IDegLira use.

The incidence of serious adverse events for IDegLira was higher than placebo and was similar to basal insulin and GLP-1.

Overall, there was a higher percentage of

dropouts due to adverse events in the IDegLira group compared to the placebo group but less than in the basal insulin and GLP-1 groups. Causes of dropouts due to adverse events are the discussed in the next slide.

Adverse events leading to withdrawal overall were low. Reasons for withdrawal in the IDegLira group included increases in lipase, nausea, dyspepsia, abdominal pain and distension which are likely attributable to the GLP-1 component.

However, the overall rate of dropout due to events in the gastrointestinal system organ class was numerically lower than for the GLP-1 group.

It is notable that there were no dropouts due to adverse events in the gastrointestinal system organ class in the basal insulin or placebo groups.

This slide shows gastrointestinal adverse reactions in the IDegLira program. Overall, gastrointestinal adverse reactions likely attributable to study drug were more common in the IDegLira group than in the basal insulin group and

the placebo group and less common than in the GLP-1 group.

Body weight increase is a risk with some antidiabetic therapies. Insulin is generally associated with increased body weight while GLP-1 agonist therapy is generally associated with modest weight reduction. In the IDegLira program, change in body weight was investigated as a secondary endpoint.

The results in the next slide were shown in the statistical presentation. I will discuss the clinical interpretation of these findings.

Across all trials, body weight changes were for the most part consistent with what could be expected from the two drug classes. In the one trial with the placebo arm, shown in the figure on the left, the IDegLira arm experienced a placebo-adjusted change in body weight of an increase of about 1.5 kilograms.

In the trial of IDegLira versus GLP-1, the IDegLira arm had a relative weight gain. In the three-arm study, the IDegLira group fell in between

the other arms in terms of body weight.

So what can be concluded from these trials with regards to body weight? Well, for one, only modest weight changes occurred in all treatment groups with small differences between groups.

For example, the amount of weight gained in the IDegLira arm and the placebo-controlled trial was about 1.5 kilograms or about 2 percent of baseline body weight.

It is important to point out that the trials did not capture the clinical meaning of these small weight differences. 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. Therefore, it is uncertain what these weight changes mean in the overall health or quality of life of subjects in these trials.

I will now turn to hypoglycemia. Hypoglycemia is a known safety issue for insulin

degludec as for all insulin products. In order to capture the risk of hypoglycemia, the FDA relies on multiple definitions to assess for risk.

The most specific of these definitions and the one which captures the most clinically meaningful events is that of severe hypoglycemia. This table shows the number in percentage of subjects who experience severe hypoglycemia including the 52-week data for study 3697. It is important to remember that the population of subjects in the IDegLira program were relatively low risk, given that they were type 2 diabetics and not on prandial insulin.

Each subject experienced only 1 event of severe hypoglycemia. And in the entire IDegLira program, there were a total of 12 events. Overall, the incidence of severe hypoglycemia was higher for IDegLira compare to placebo or GLP-1 analogues.

However, there were too few cases to differentiate any clear difference between IDegLira and basal insulin.

The percentage of patients who experienced a

hypoglycemia event using the Novo Nordisk confirmed definition for each phase 3 trial is shown here. The applicant conducted analyses of treatment differences for two of the trials.

The applicant's analysis showed less hypoglycemia for IDegLira versus the IDeg and glargine comparators for Trials 3697 and 3952 respectively.

For trials where IDegLira was compared to a GLP-1 or placebo, Trials 3697, 3851, and 3951, the proportion of subjects experiencing hypoglycemia was higher for IDegLira than for GLP-1 or placebo.

We also examined the ADA documented symptomatic hypoglycemia definition, which requires a plasma glucose less than or equal to 70 milligrams per deciliter accompanied by symptoms.

The pattern of treatment differences for the ADA documented symptomatic definition was somewhat similar to the Novo Nordisk hypoglycemia definition, but the differences between arms within trials appear to be attenuated.

Again, for trials where IDegLira was compared to a GLP-1 or placebo, Trials 3697, 3851, and 3951, the proportion of subjects experiencing hypoglycemia was higher for IDegLira than for GLP-1 or placebo.

In trials where IDegLira was compared to insulin with no dose cap, Trials 3697 and 3952, the differences between study arms were less apparent using the ADA documented symptomatic definition.

Specifically, the proportion of subjects expecting hypoglycemia was similar between IDegLira and IDeg in Trial 3697. And in Trial 3952, the difference between arms was smaller.

Overall, there were few events of severe hypoglycemia. The Novo Nordisk definition showed less hypoglycemia when compared to insulin comparators. The finding was attenuated using an alternative definition, specifically the ADA documented symptomatic definition. And in both definitions, IDegLira had more hypoglycemia than placebo or GLP-1 comparator.

There are limitations to the hypoglycemia

analysis. First, hypoglycemia definitions other than severe may be subject to reporting bias in open-label trials.

Second, if the definition does not require symptoms, then the endpoint is based on glucometer-derived data that are subject to reliability issues for point of care devices.

Third, trials did not capture the clinical meaning of observed differences in hypoglycemia rates based on definitions other than severe. There was no apparent difference in the risk of severe hypoglycemia by treatment.

It is uncertain what these data mean in the overall health or quality of life of subjects in these trials.

In regards to other safety findings, pancreatitis and thyroid neoplasms were rare with no clinically significant difference between IDegLira and comparators.

IDegLira, similar to liraglutide, had a 2- to 3-heartbeat increase compared to placebo. The cardiovascular safety of liraglutide is being

investigated in the outcomes trial and is not a topic for discussion today.

There were no clinically important differences of immunogenicity or injection site reactions for IDegLira versus comparators.

In summary, the IDegLira program consisted of five phase 3 trials that met statistical superiority over comparator for hemoglobin A1c. The applicant met the pre-specified glycemic endpoints.

There are questions regarding the external validity of these results due to issues of the trial designs of the capped trial and the insulin comparator dosing in the non-capped trials. The generalizability of the trial findings to clinical practice is a discussion topic for the committee.

Also, the product presentation of IDegLira as a fixed-combination drug does not allow for the two drugs to be dosed individually, which is different from the way Victoza and basal insulin are currently used in clinical practice, as two separate products.

A trial comparing IDegLira to use of the individual components separately was not conducted nor required to inform whether there are potential benefits or drawbacks to this approach.

With regards to dosing of the liraglutide component, for previous insulin or GLP-1 users, a reasonable proportion reached liraglutide doses of at least 1.2 milligrams. For patients not previously treated with insulin or GLP-1, the proportions were lower.

In regards to safety, the safety profile of IDegLira reflects the profile of its components. In particular, weight gain and hypoglycemia from its insulin component and gastrointestinal adverse reactions and heart rate increases from its liraglutide component. There were no unexpected safety issues identified.

Potential safety issues related to the product presentation will be discussed in the next presentation. Thank you for your attention.

FDA Presentation - Ariane Conrad

DR. CONRAD: Good morning. My name is

Dr. Ariane Conrad and I am 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 degludec liraglutide, which I will refer to as IDegLira for this presentation.

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

IDegLira is a fixed-ratio, multi-ingredient product that contains a long-acting insulin, insulin degludec, and a GLP-1 agonist, liraglutide, in a single pen device.

The pen device will contain 100 units per milliliter of insulin degludec and 3.6 milligrams per milliliter of liraglutide and deliver doses from 1 to 50 in a single injection. Each increment will contain 1 unit of insulin degludec and 0.036 milligrams of liraglutide. The pen uses the same FlexTouch device platform that is currently used

for other marketed products within the applicant's product line.

Pictured here is a sample pen injector provided by the applicant to aid in the review of the product. The picture depicts what the pen looks like in the dialed position for dosing. And you will notice that the dose button for this device does not extend when the dose is dialed.

In the process of reviewing this product, we identified a number of aspects to consider for IDegLira. First, the two active ingredients in this product are dosed using different terms of measure, units for the insulin component and milligrams for liraglutide.

However, the pen device dials doses based on the units of insulin alone without indicating the respective liraglutide dose. In addition, the applicant is proposing to communicate the dose without using any terms of measure in the labeling.

Designating the dose without using terms of measure and conversely, the use of the term "units" in labeling could potentially mislead practitioners

since neither designation references the product contents, meaning the lack of units doesn't indicate what the product contains and the term "units" only references the insulin component without indicating the presence of a GLP-1 agonist.

The use of both dosage terms, units and milligrams, would likely be confusing for users. But the best strategy is unclear based on the data that we have available.

Of note, we have requested that the applicant conduct a labeling comprehension study to test their proposed product labeling. The results of the study should help to determine if users will be able to understand how to prescribe the product safety and use the labeling methods proposed.

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.

Third, we identified that there was a dosing limit of 50 units of insulin degludec for this product due to the maximum recommended dose of

1.8 milligrams for liraglutide when used for glycemic control.

Considering that type 2 diabetes patients may require insulin degludec doses over 50 units, prescribers may attempt to prescribe doses larger than this since it 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 conducted 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 include 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 so that the study population for a human factor study would be much smaller than those expected for clinical trials.

In addition, testing should include all critical tasks necessary for safe use of the device, the final product design, and the 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 to 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 is very small, even one error could identify unexpected use behavior that was not previously identified during the 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 factor studies can indicate a problem with the product's design or labeling that we would expect will be problematic with actual use by a larger number of users.

Now, I will review the human factor study that was conducted for IDegLira. The applicant conducted a study designed to evaluate the ability of the intended users to properly use the IDegLira pen by evaluating all the tasks necessary for the injection process, including dialing and administering a dose.

The device usability study was conducted with 16 physicians, nurse practitioners and physician assistants, 15 pharmacists, 15 nurses, 64 adult patients with diabetes, and 64 elderly patients with diabetes to determine their ability to properly use the pen injector.

Training on the product was provided to 63 of the patient participants prior to starting the study. This training included a 30-minute hands-on session with a certified diabetes educator

and the use of a training video.

None of the healthcare providers included in the study received training on the medication or pen injector prior to completing the study tasks.

The study was designed to simulate use tasks and provide data to support that intended users can dispense, differentiate, prepare, and administer doses by having study participants complete product differentiation tasks, handling tasks, and evaluation of the instruction for use or IFU.

The product differentiation tasks were separated into two parts. First, all study participants were presented with a variety of pen injector cartons and instructed to select the test product.

After those selections were made, study participants, excluding the pharmacists, were presented with a variety of pen injectors to determine if they could select the IDegLira pen.

For the product-handling component of the study, the study participants, excluding the pharmacists, were presented with a carton of

IDegLira pen injectors, the instructions for use, and other materials needed to simulated injection administration, including injection cushions, needles, and sharps containers.

In addition, all the trained participants and six of the untrained participants were asked to interpret two excerpts from the instructions for use after completing the hands-on tasks to demonstrate understanding that the dose prescribed will equal the number displayed in the dose counter and how to set the prescribed dose on the pen using the dose selector and dose pointer.

The IFU evaluation included six untrained participants because these were the only participants in the untrained armed that actually used the instructions for use during the study.

Now, we'll provide a summary of the study results. Errors occurred in the differentiation tasks. However, most of these failures were considered study artifacts since they occurred due to participant confusion of the task rather than poor differentiation among the products.

These errors were noted to have occurred due to participant confusion regarding the tasks, which led to incorrect carton and pen selection.

Failure to prime the pen and failure to prime the pen correctly were the most common errors noted during the product handling tasks. In actual use, we would expect that these errors would result in small under-doses that would be considered clinically insignificant.

The applicant has indicated that they will mitigate for the potential for this error by increasing the prominence of the priming instructions in the instructions for use. But we acknowledge that priming errors are common to this device platform.

For the instructions-for-use evaluation exercise, all the trained patient participants and the six untrained participants that use the IFU demonstrated that they understood that the dose prescribed equals the number displayed in the dose counter and they displayed they understood how to dial the prescribed dose on the pen using the dose

selector and dose pointer.

We requested that the applicant also complete a labeling comprehension study for IDegLira to evaluate whether prescribers will be able to appropriately prescribe and dose this product.

This additional study was requested to address the concerns regarding the risk for medication errors during the prescribing of IDegLira since the product represents a change to the treatment paradigm for diabetes. And the multi-ingredient content of the pen may not be easily recognizable by prescribers.

The applicant submitted the proposed protocol for the study for our review in March and proposes to conduct the study with at least five of the following subgroups: endocrinologists, primary care physicians, nurse practitioners, and physician assistants.

The applicant intends to introduce study participants to the drug and the prescribing information, then ask them to read and perform

knowledge tasks based on three individual patient profiles for each of the three therapy options available to use IDegLira per the prescribing information: as add-on therapy to oral antidiabetic agents, converting patients to IDegLira from other GLP-1 agonists, and converting to IDegLira from basal insulin.

If study participants provide responses that are not in line with the recommendations provided in the prescribing information, they will be asked some follow-up questions to obtain subjective information regarding their errors. We plan to review the pending labeling comprehension study results when they are available.

In summary, while errors did occur, the human factors data indicate that users were able to use the pen injectors. The errors that did occur were common to this device platform and to pen injectors in general so we do not feel that the risk associated is serious. We feel that this risk is minimal with this device and can be addressed with improvements to the product labeling.

However, we are unable to determine prescriber ability to comprehend the dosing recommendations and the prescribing information since this data is not yet available for our review.

This ends my presentation. Thank you for your attention.

Clarifying Questions to FDA

DR. SMITH: Thank you. So again, we have time now for clarifying questions. And I think we should try to focus those particularly on the FDA but ultimately, both the FDA and the sponsor will have more time for that this afternoon.

Dr. Nason?

DR. NASON: Thanks. I wanted to ask a question about the time to dose stabilization calculations. It seems like that's a bit of a mixed bag, a bit hard to interpret because it seems like your dose could stabilize either because you hit the maximum dose either for the capped insulin or for the pen.

I was wondering if you'd separated that out

at all. You could either have hit the maximum dose or you could actually be within the target and therefore not increasing the titration anymore.

I was wondering if any of those analyses had been done, sort of separating those types of stabilization between people who hit 50 on either the IDegLira or on the insulin itself when it was capped versus people who stopped increasing their dose because they were at the target.

A sort of related question, which I'm not sure exactly who might answer, is I'm just wondering if there's any data available on people who do use both of these in actual practice already as far as what doses those people are taking, if those people tend to be up at the high end of the 50 and the higher end of the lira dose or lower, when people tend to take them in combination, if they tend to be at lower doses.

DR. YANOFF: So with regard to your first question, I may need a little more clarification of what you're looking for.

We looked at the trials individually. We

didn't pool data among the trials. So there was only one trial that had a dose cap and so we looked at that trial separately from the ones with the cap. So we really didn't make any conclusions that would sort of integrate that data where we would need to separate it back out.

DR. GUETTIER: So let me maybe answer that question. I think I know what you're asking. It really depends on whether or not Dr. Kettermann has actually looked at that.

So I think, on some of the figures that Dr. Condarco showed, you can tell the proportion of people who actually met the goal, the SMPG goal. And for all these trials, it was in the never above 50 percent who met the goal. So at least, we have some of that answer.

I don't know if Dr. Kettermann actually looked at the proportion who actually dose stabilized because they reached the maximum dose of the product, and perhaps the applicant has that data if we don't have it.

MS. KETTERMANN: I think it's a great

question. We looked at how many subjects hit the maximum dose. And this is on slide 37. It's 67.9 percent on IDegLira and 70.9 on IDegludec.

DR. NASON: Okay. Thank you.

DR. GUETTIER: And then for your second question with regards to concurrent users, we got our drug-use folks at the FDA to try to look into this question. But it's almost impossible to find out exactly what doses concurrent users are taking from our drug use data because those data are not captured in drug use.

DR. MATHEW: Hi. My name is Justin Mathew. I can briefly go over the drug utilization data that we do have.

So to determine the nationally projected utilization of GLP-1 agonists in the U.S. outpatient retail setting, we used the IMS, Vector One: Total Patient Tracker. It's a national level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

This graph shows the total number of nationally projected unique patients who received a dispensed prescription for GLP-1 agonists, stratified by product from April 2010 through March 2015 in 12-month increments.

Looking at the solid gray bars, you can see that there was a 65-percent increase in the number of patients who received a dispense prescription for GLP-1 agonists from approximately 535,000 patients in the first time point to 882,000 patients in the 12-month period, ending in March 2015.

Focusing on the most recent 12-month period, from April 2014 through March 2015, Victoza was a market lead, accounting for approximately 68 percent, followed by Bydureon with 20 percent and Byetta with 12.5 percent.

We also looked at a sample concurrency analysis and we used the IMS Health Real-World Data Adjusted Claims U.S. Database, which is a longitudinal patient-level health-plans claims database capturing a sample of U.S. commercially-

insured patients.

So this graph shows a sample proportion of GLP-1 agonist patients who also had a claim for basal insulin from April 2010 through March 2015, again in the same 12-month increments.

The proportion of patients who had a claim for GLP-1 agonists and also had a claim for basal insulin increased from 17 percent in the first study time period to 27 percent in the 12-month period ending in March 2015.

We couldn't find the specific actual doses. Our database wouldn't allow us to look at the specific dosage points for the top end, as your initial question asked for.

DR. SMITH: Dr. Yanovski, did you have a question relevant to the same point?

DR. YANOVSKI: Yes, I did. It was related to the longer titration time for the people in the uncapped insulin degludec and the fact that the glycohemoglobin at the end of 26 weeks might not really reflect the titrated dose.

My question is, Pivotal Trial 3697, I

believe, had a 26-week extension for all of those components. I didn't see any of the data presented from that. Could that help answer what happened over a longer time period regarding titration and change in glycohemoglobin?

MS. KETTERMANN: I think it's a great question. Yes, we have data in 52 weeks, but the last 26 weeks were extension of the trial and that is why it had a large dropout. It was 20 percent dropout and that is why it was not equivalent to the first part of the trial. And it was not evaluated as a regulatory endpoint.

DR. YANOFF: We did look at some exploratory analyses of the 52-week data. And while it appears the trend may continue, the difference may continue, the tipping-point analyses and other analyses assessing for this large amount of missing data were not as robust.

So we couldn't make firm conclusions about whether the difference would have been seen at 52 weeks if that had been the primary efficacy endpoint.

DR. GUETTIER: I think what you can also see and appreciate from the graph is there seems to be titration fatigue in all these trials, where at some point, the dose stops increasing for whatever reason. And we're not really sure because the reasons for why the dose stops is not obvious.

So that's another issue to consider. I mean the rate of rise and dose is steep early on and then seems to flatten out in all these trials for some reason.

DR. SMITH: So I have a question that I'll start with the FDA but possibly the sponsor can help with. In the FDA briefing document on page 64, there's a table 17.

Within it, what this does is provide a summary of gastrointestinal events. In the total events, as was discussed in the presentation, there's a somewhat lower percentage rate of events with the IDegLira versus the GLP-1. I'm interested in those two columns. But when I actually look at the breakdown on that, there is a substantially higher rate of diarrhea, nausea, and vomiting with

the GLP-1 analogue group.

But then there's a long list of individual-reported events, many of which are small numbers, 1, sometimes 3 or 4. And from the data that are available, it's not really possible to know whether that's a small number of individuals with multiple reports or whether those are multiple individuals.

But I noted within that there are a number of those that might be interpreted as inflammatory and why that should occur, I have no idea. But they include colitis, esophageal disorder, duodenitis. Many of those are an N of 1. And these are all essentially present in the IDegLira and for the most part not present in the GLP-1 group.

They include enteritis, where there's 4 in the IDegLira and there are none in the GLP-1 group. Esophagitis is 3 in the IDegLira and none in the GLP-1. And I just want to make certain that we're not missing something.

My question is really sort of two-part. You

don't have to have an immediate answer for this. We can look at that later. But the question is basically how much of that might represent multiple reports within a single or a very small number of individuals, so something like duodenitis and colitis get reported in the same one individual.

Also, the question is, if there were an effort to combine those reports into ones that may make some logical sense as, for example, an inflammatory process in the bowel, what those numbers might look like.

Again, I don't have a particular concern because I don't see a mechanism that should explain this, but I'd like to make sure we're not missing something by over-fragmentation of what's actually reported.

So do you have any comment on that now or is that something that perhaps could be looked at and we could come back to this afternoon?

DR. YANOFF: I think at this time, the only comment I would make is just note that the almost three times as many patients in the exposure to

IDegLira versus GLP-1 in that table, and I'm thinking that might be something to consider. As far as how many individual patients this represents, I would request the applicant please address that.

DR. SMITH: So I'm really looking for reassurance on that in terms of some breakdown, better kind of breakdown or clustering of those numbers.

Is that something you might be able to either comment on now or review a bit? I'd be happy to talk to you about it a little bit more offline and then maybe come back this afternoon.

DR. GOUGH: We can try and get that information for you after the break, if that would be helpful.

DR. SMITH: Okay. Thank you.

Dr. Wilson?

DR. WILSON: So my question builds a little bit on what Jean-Marc Guettier was talking about. There's a whole series of slides starting with the FDA slide 60.

I'm trying to understand the 40-percent number. And so what happened starting at about week 10 to 12 and those who were getting the IDegLira? So they don't keep increasing their dose and they're at 40 percent.

Does this take into account intention to treat? Is that number actually bigger for those who are still in the trials? And then can anybody tell us about the perhaps 40 to 50 percent who are not represented? Who are the other groups, the people for instance?

Since only 40 percent are reaching glycemic goals, what are the others like? Are they still participating in the studies; they're just not doing everything they're supposed to be doing?

DR. CONDARCO: Thank you for that question. In terms of these graphs, they were obtained on an information request from the sponsor. And specifically to just focus to what they say, they're not cumulative; they look at each specific week.

So a patient could have been listed in week

2 and then still been listed in week 10 but maybe didn't reach goals in week 11. In terms of what the patients who did not reach goals, I don't have an answer for that in particular.

We did look at the hypoglycemia to see whether or not there were issues with hypoglycemia and perhaps this is why they weren't reaching goals. I mean, the analysis, based on severe hypoglycemia, did not suggest that this was the reason why they weren't reaching these goals.

DR. WILSON: As a follow-up, Dr. Jean-Marc Guettier had said you've seen this before. Is this 40 percent what you would expect from studies like this? Would you expect a higher percentage reaching goals?

DR. GUETTIER: I think it really depends on what Dr. Condarco said in her presentation. It really depends on the algorithm. I think it depends on many things; population you're starting with, the algorithm and how aggressive the algorithm is, the investigators, whether or not they're actually following the algorithm or just

doing what they're going to be doing anyways in practice.

Again, with titrations, always, what we see is early on, there's an effort to titrate which kind of dissipates as the trial is ongoing. Part of that may be because some people are reaching goals. Part of that may be because people are not tolerating the drug, but that's not captured, so we can't tell why.

Ultimately, you know that you're at the right dose of insulin if either you can't tolerate the drug anymore because you've reached severe hypoglycemia or because you've actually reached your target.

So if that's not happening in these trials, then we have issues interpreting what the efficacy means in these trials. And oftentimes, we don't really have the data to say what's happening.

DR. GELATO: So how does that relate to 80 percent of these patients reaching their hemoglobin A1c target? Because clearly, only 40 to 50 percent are reaching --

DR. GUETTIER: Right. So what you're looking here is the SMPG targets. So that's the self-measured plasma glucose, which is what's used to titrate the dose.

Again, I think the population matters. If you start off with a population at 8 percent, you're going to get a lot of people to 7 percent. If you start off with 12 percent, you might not.

So this, again, has to be interpreted that way. This is not 24-hour glucose goals. And HbA1c would capture a more global picture of glucose control over 24 hours.

DR. SMITH: We're going to need to break for lunch in a couple of minutes to keep us on schedule. We're going to have more time for these questions this afternoon.

But I would particularly like to ask the panel if there are any panel members who have a question that might require some background work by the FDA or the sponsor to maybe research some data or present some data a different way, I'd like to give you a priority to ask that question before we

break for lunch. So anyone in that category?

Dr. Nason?

DR. NASON: I'm not sure if it is or not, but related to this and follow-up to my original question, you showed me where the number of people or the percent of people who hit the maximum for that one study are.

But for the IDegLira, for the other studies, is it possible to know how many got to the maximum dose for the other, especially phase 3 studies? Because it certainly could relate to this question about why they're not continuing to titrate up if 70 percent have hit the 50. I don't know if that's information you already have or not.

DR. YANOFF: To clarify your question, you're asking about the 50 for the IDegLira arm because --

DR. NASON: Yes.

DR. YANOFF: -- only one trial had the 50 cap for the comparator.

DR. NASON: Right.

DR. YANOFF: So you'd like to know for the

IDegLira arm?

DR. NASON: Yes. So for that trial, both numbers were given, how many people maxed out on both arms? And I just was asking for the IDegLira on the other trials, how many people maxed out.

DR. YANOFF: So we don't have the percent maxing out. We have the insulin dose by week again correlating with the comparator arm on that figure. So you can kind of get an idea. The average was about 40 units by the end.

If the sponsor could provide the proportion reaching 50, that would be helpful.

DR. SMITH: We're getting ahead now, so is that something you have right now or we'll come back to that.

DR. GOUGH: Can I just clarify the question? Are you asking for the proportion of patients that achieved the maximum dose of 50 in each of our trials? Because we can provide that information.

DR. NASON: Yes. It's a question [inaudible - off mic].

DR. GOUGH: So the numbers that get to a

maximum dose of 50 for each of the trials, we can bring to you after lunch.

DR. SMITH: Any other questions on this same line?

DR. GOUGH: Or I can show you. Okay.

DR. YANOFF: One clarification. Would you like to know the time point when a certain proportion reached 50 or how many reached 50 units at 26 weeks? Would you like any more granularity on that issue?

DR. NASON: I think it's interesting information because certainly, in the one where it was provided, there was a big jump in the time to dose stabilization which I think is most people hitting 50 just from my rough calculations.

So it's an interesting issue if that's sort of a time point where, at 10 or 12 weeks, most people are at 50 and they can't keep going up as opposed to titrating up slower, but I think it informs this question about why they stop titrating.

DR. SMITH: Dr. Wilson, do you have a

similar point?

DR. WILSON: Yes. The question is, if they can do that, I would be very interested. I think it would help us to understand who cannot get to 50.

So for instance, a patient who weighs 300 pounds who has a lot of insulin resistance starting at 16 units and then titrating up over 26 weeks, I'm guessing already that patient is not going to be able to get there with a combination drug.

So something about the obesity status for those individuals would help. Their body mass index at entry for those who went over 50 and were not able to do it. Is my question clear? I think they probably have that information.

DR. SMITH: I think the sponsor needs to answer that. Whether they understand what they need -- is that clear, what Dr. Wilson was just looking for?

DR. GOUGH: So you would like to see body mass index in relation to final

dose -- sorry -- those patients that reach a maximum dose of 50? So those that get to maximum dose of 50, do they have any characteristic body -- yes.

(Dr. Wilson nods yes.)

DR. SMITH: Ms. Hallare, did you have a question?

MS. HALLARE: I would just like to confirm if there is no concern with regards to renal function and if there have been any effects of IDegLira on people with mild or moderate kidney impairment so that they may be a subgroup to check with regards to how much would be given for the subgroup.

DR. SMITH: That's for the sponsor, I believe.

MS. HALLARE: It's more for the sponsor, but I think it's also for the FDA if they have any concerns with regards to renal function.

DR. GOUGH: Again, can I clarify exactly what it is that you want? Because we can break our data down by mild and moderate renal impairment

within our clinical trial program. What specifically would you like to see in relation to renal function?

MS. HALLARE: For instance, for people with mild or moderate kidney impairment, for instance, if they have had increase in adverse events or also exacerbation of kidney function and also, for those who are normal, for instance, if there's any new renal malfunction cases.

DR. GOUGH: So you'd like to know if there's any deterioration in renal function and also whether there are any adverse events or whether the adverse events are associated with impaired renal function. We can bring you those data as well.

DR. SMITH: Okay. We're going to do one more question, and then we're going to break for lunch.

Dr. Gelato, you have the last question here. Got answered? All right.

So I think we're going to take a lunch break right now. Again, we're going to reconvene here in one hour. So we'll come back here at 1:10. Please

take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch among yourselves, with the press or with any member of the audience.

Thank you. We'll see you at 1:10.

(Whereupon, at 12:10 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:10 p.m.)

Open Public Hearing

DR. SMITH: So welcome back to everyone. We're now going to have the open public hearing portion of this session today.

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 speak only when recognized by the chairperson.

Thank you for your cooperation.

Will speaker number 1 now step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. CLOSE: Sure. I think I have some slides actually that we confirmed earlier. Is that right? Thank you.

Hello, my name is Kelly Close. Thank you so much for the chance to speak today. I'm founder of the diaTribe Foundation, a non-profit focused on improving the lives of people with diabetes and pre-diabetes. I've had diabetes since 1986.

By way of disclosure, our biggest funder is the Helmsley Charitable Trust and we're also supported by hundreds of patients and dozens of non-profit and for-profit organizations, including today's sponsor.

I also founded Close Concerns in 2002 and my colleague, Emily Regier, will be giving her disclosures in her talk in a few minutes. She's the 12th speaker.

So my number one message today is that the

healthcare system is changing dramatically and it's more important than ever to strengthen, to understand, and to seek to optimize the lives of people with diabetes and their healthcare providers.

Giving people with diabetes the option of taking one combination drug instead of two separate drugs is one really great way of addressing this. That really can improve lives and outcomes.

The FDA has so much to be proud of in its approval of great innovations for patients over the years and that's especially considered how under-resourced you are. And I don't think everyone always acknowledges that or understands that.

But all too often, those drug innovations haven't realized their full potential because they don't fit well enough into all patients and all healthcare providers' lives. On the doctor and nurse front in particular, mealtime insulin doesn't really fit so well into their workflows and that's increasingly true today.

By offering a simpler, easier, better way to use a GLP-1 agonist and insulin, Xultophy addresses both of these problems of patient challenges that are beyond the therapeutic challenges and doctor problems that reflect an increasingly challenged modern healthcare system in America.

I'm standing here today because I strongly believe that Xultophy has a better chance than the current standard of care, which isn't good enough anymore, to achieve what we all want for people with diabetes: better health and better quality of life.

With better quality of life, I think I saw some of your ears perk up. I might have even some frowns, some imperceptible. Although better quality of life isn't officially associated with better adherence, and although better adherence isn't officially associated with better long-term results for people with diabetes, and even though we aren't even going to talk about the fact that adherence studies are really hard to design and to fund, I really hope that you'll consider the tie.

Randomized-controlled trials are so value for so many different reasons. But from a patient perspective, we want to think about what real life will be like when we take therapies.

With Xultophy, I feel like real-life impact could be disproportionately positive given a bunch of different things up here: It's one injection; it's one co-pay. That may not be your most important thing because you may think that co-pays are beyond your domain and that's not right. That's not right.

Here's a different perspective. If this drug is approved but patients can't access them, they may as well not be approved. And anything that you can do to improve this, even in a small way, reducing number of co-pays, is positive.

What else is up there? There's less hypoglycemia. There's less worrying about hypoglycemia. There's no weight gain that happens here after you're -- in fact, with this therapy, there's actually weight loss for many patients.

All of these reasons could make it easier

for patients to take the next step in their treatment and to be successful in their diabetes management and easier for doctors and nurses to help them be successful.

That's just another slide with a shocking statistic explaining the real life of a pretty amazing therapy.

Another word about doctors and other healthcare providers, we know most providers are pressed for time; they're under huge pressure; 11 minutes is as little as appointments can take. That doesn't even begin to acknowledge the huge administrative pressures they feel.

Better, easier, longer-lasting treatment can dramatically help address this crisis, not only that current doctors have so little time, but also that so few new doctors are going to into this field.

At a time when the number of people needing help is exploding, the number of people wanting to go into this field to help us is actually staying neutral or going down.

Today, you have this historic opportunity to approve a drug that has a great chance to increase patients and providers' willingness to take the next step in their treatment plans.

By offering a more efficient, user-friendly, better way to advance care for patients that need more advanced treatment, Xultophy can change the landscape of type 2 diabetes management and improve life for millions of patients.

Don't you want that to happen on your watch? I hope so. Thank you very much from the diaTribe Foundation.

DR. SMITH: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. TASIK: Good afternoon. Thank you for allowing me to present today. My name is Christopher Tasik, and I was diagnosed with type 2 diabetes about 18 years ago.

I'm disclosing that Novo Nordisk has paid my travel expenses to be here to testify today. I am

self-employed and I have chosen to take a day and a half away from my businesses to come here because I feel so passionately about the good work that the FDA and the companies like Novo are doing to advance patient care and extend the lives of diabetics like me.

As a type 2 diabetic, my presentation will not be evidence-based but instead draw on my personal experience living with this disease for almost 20 years.

I believe it's through this work and through discussions similar to today's that patients have come to enjoy new treatment benefits. Patients and researchers share the common ultimate goal of lowering our A1c and controlling our blood sugars.

However, the day-to-day experience of patients versus the scientific community represented here today could not be more different in my opinion.

A medication like IDegLira represents not only a new and exciting opportunity to achieve better control for patients, particularly those on

dual injectables.

For those of us, like myself who take the two underlying drugs that are in IDegLira, it would represent 365 less self-inflicted needle punctures per year.

While I don't like needles or needle punctures, I'm not afraid of them, although I've spoken with many diabetics who are terrified of them.

So while the scientific community measures success via clinical trials, we patients add in that extra layer of less pain, less bruising, and, for some, less daily fear to get to the same shared goal of better glucose control.

In terms of cost, personal experience, my co-pay has went up with our prescription plan this year over 500 percent, so a dual injectable therapy now costs me $2,000 out of pocket per year.

With a combined therapy, that would bring my cost down dramatically and cut that in half to $1,000. Last year, the two drugs combined cost me $400 for the year as a therapy. So it's a

meaningful difference in terms of cost for patients.

Most diabetics are very committed to doing what it takes to treat our disease. From diet and exercise, to regular doctor visits, to taking our medications on schedule, we all have our routines.

However, it's a progressive disease and most of us outgrow medications as we age. Many go beyond the limitations of oral treatments and are using combined therapies.

We need companies like Novo working with the FDA to bring new treatments to market to keep us healthy.

When I was initially diagnosed, there were a handful of prescription oral medications that could be taken, testing devices that were very basic. They used rather thick needles and required, by today's standard, a significant amount of blood per test.

My main objective as a type 2 diabetic is to control the disease so I don't suffer from potentially devastating long-term complications.

I'm 46 and have an 8-year-old daughter and a 12-year-old son, and intend to live a very long life.

However, my ability to do so depends on two things, how well I take care of disease and, equally important, active research and development for new treatment pathways and options and hopefully a cure to type 2 diabetes in my lifetime.

Over the past 20 years, I've witnessed remarkable improvements in treatment technology due to research and development that has been done to better control blood sugar. There are many new oral and injectable medications that may not have been imagined 20 years ago. Testing is easier, more convenient, and less painful.

The future is incredibly bright with lots of new medications and other technologies, including non-invasive testing that I think are coming to the fold in smart-based phone technology.

None of this would be possible without the support for research and development and a process to bring the best of these ideas to the hands of

patients like me.

Speaking on behalf of all diabetics, I would like to thank you for your time today and encourage you to support this continued contribution to research. Thank you.

DR. SMITH: Thank you. Will speaker number 3 now please step up to the podium? Please introduce yourself, state your name and any organization you are representing for the record.

(No response.)

DR. SMITH: Speaker number 3?

(No response.)

DR. SMITH: Okay. We'll move on. Speaker number 4 would step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SCHWARTZ: I'm Dr. Stan Schwartz. I'm representing AACE today, American Association of Clinical Endocrinologists, the world's largest organization of clinical endocrinologists, where we're committed to enhancing the ability of its members to provide the highest quality of patient

care.

My personal background is here. There we go. The company has not spoken to me or to the AACE board in regards to what we are saying today.

We emphasize that those with type 2 diabetes -- I'm not going into detail, but it's amazing how much it affects individuals in our society.

With regards to the agent we're discussing today, the patients and physicians need more choices to control the burdens of diabetes. For patients that require insulin, there's a logic for basal insulin with GLP-1 receptor agonists.

They decrease required dosing basal and multiple mechanisms are involved. It can decrease hypoglycemia by both decreasing dosing basal and potentially the need for bolus insulin, avoids weight gain and engenders some weight loss in some situations and decreases glycemic variability.

It gets more patients to goal with less medications by reducing the number of meds combined with basal in order to get the glycemic control and

again by avoiding bolus insulin. And thus, it reduces the medication burden and likely the cost as well, we hope.

On the lower portion of this slide, the multiple mechanisms that destroy the beta cell are published. This is a beta cell centric classification of diabetes and diabetes care; leads to the abnormal glycemic control and complications in micro and macro-cardiovascular disease. On top are the same mechanisms that lead to macrovascular damage and this provides a logic for treatment in the real world.

AACE specifically has principles as part of a comprehensive type 2 diabetes management algorithm. I'm just going to highlight that we aim for the lowest glycohemoglobin possible. As well as we're not using hypoglycemic agents, we need to individualize our therapy.

We pay special attention to avoiding hypoglycemia and weight gain. And whether you use the frontal octet [indiscernible] or you'll see in a moment my egregious 11, we want to use the least

number of agents that treat the most number of mechanisms of hypoglycemia without hypo, without weight gain, and by preserving the beta cell.

The hypoglycemia issue is absolutely critical. We know hypoglycemia can lead to acute cardiovascular events in type 2 diabetes. This is a study that included type 2s on sulfonylureas or insulin.

We know the mechanisms that are involved. I won't detail them, but basically they increase the risk of arrhythmias, and reduced coronary artery blood flow, and sudden death. What's maybe scarier is that many hypoglycemic episodes are unrecognized.

This is your hypoglycemia unawareness. Forty-seven percent of patients with type 2 diabetes in the study with continuous glucose monitoring show unrecognized hypoglycemia often at night. It puts into question any of the reports of hypoglycemia in all these studies. It's likely to be greater in general.

So the visual translation of our algorithm

is here. We believe in early combination therapy over 7.5 [ph]. We believe in sulfonylurea therapy last, if at all.

My personal bias is that we shouldn't use them ever and we should, in regard to the other agents, match the right drug to the right patient, and you'll get the individualized approach. Then if we add basal insulin, you have a choice of continuing these non-insulin therapies. And this was the first diagram that, along with ADA, about the same time, suggested that maybe we should --

DR. SMITH: For time reasons, if I could ask you to just maybe summarize in like one sentence because we really need time to include the others.

DR. SCHWARTZ: Okay.

DR. SMITH: Okay. So just maybe a one-final sentence summary would be help for us.

DR. SCHWARTZ: So basically, we don't want to use insulin until we have to, and if we have to, we're going to use a combination drug to minimize cost, minimize the complications of diabetes, and our patients will be the benefactors. Thank you.

DR. SMITH: Okay. Thank you.

So will speaker number 5 now please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. COLLAZO: Hi. My name is Liz Collazo, and I'm a person with type 2 diabetes. I am also a freelance writer and a blogger at Type 2 Angry Diabetic. I am here today of my free will, except that I am being provided for my travel expenses by the diaTribe Foundation.

Now, as a person with diabetes and as the daughter of a person with diabetes, I am very anxious to speak before you today, but the level of anxiety that I am feeling right now is nothing in comparison with the anxiety that a person, including my own father, felt on the very first day that they were told that they needed to go on insulin and that is because a medication such as insulin carries with it a great deal of myth, stigma, and concern.

Persons with diabetes often work hard to

make changes in their lives such as weight loss and various other lifetime changing situations. And when they are told that they need to go on a medication that could potentially put all of that jeopardy, there is a loss of trust and confidence in their own management of their condition.

For years, my father avoided going on insulin and life-saving medications because of these fears he had. These fears hurt and damaged his health for the long term. If he had had access to combination therapies, combination therapies such as the medication that we're considering today, he would probably would still be alive today.

You see, unfounded or not, the fears that my father hard are still very prevalent in our society regarding diabetes and medications. People have to consider things like weight gain, hypoglycemic incidents, and the fear of confusion with managing multiple types of medications and dosing multiple types of medications.

I know that we consider often how well is

this medication going to stack up against another medication, but we also don't tend to consider the psychosocial effects of how well is a person going to have the confidence to manage their own condition.

I believe that Xultophy is the kind of medication that could help rein in many of those fears. This medication could help people take ownership of their well-being, not feel like they're sacrificing their well-being.

We have to ask ourselves, do we want people thinking that they're sacrificing their well-being? When we have more options for people, we open up the floodgates of confidence for people to take ownership of their diabetes management.

While it is true that there are a lot of potential secondary side effects to medications, there is also the possibility of increasing patient engagement in taking care of their diabetes regime with this medication.

While there are limitations, while there had been limitations in past generations, I would like

to encourage you to giving people possibilities for the future for managing diabetes.

I include those possibilities for myself. I work very hard to keep my A1c at below 6 percent and that's not something that's very easy. And I'd like to be able to keep doing that for the future.

Thank you very much for your time.

DR. SMITH: Thank you.

Will speaker number 6 now please step up to the podium and introduce yourself? Please state your name for the record and any organization you are representing.

DR. Norwood: My name is Paul Norwood. I am from Fresno, California. I'm a clinical investigator. I've been a clinical investigator for 24 years and participated in innumerable clinical trials. I'm also an endocrinologist for 30 years and I take care of over 2,000 diabetics.

My flight and room and board for two days have been paid by Novo Nordisk, as you well know that I've also traveled 14 hours to get from Fresno for this four minutes. I'm also paid as a

principal investigator by Novo Nordisk.

In Fresno County, we have 46 percent Hispanics, 44 percent Caucasians and 10 percent Asians and blacks. And 10 percent of our patients, 1 out of 10 people, have diabetes because we have so many Hispanics.

I have already used liraglutide and degludec as individual medications in patients with great benefit. This is my experience.

At first, I looked at this medication and I thought they were actually joking because, why wouldn't you want to give the maximum amount of Victoza instead of dividing up the dose with the 50 units?

But I was proven to be wrong and my skepticism was wrong. The stuff works and it's nice. It has certain benefits of less insulin used, less hypoglycemia, and, of course, some weight loss.

Why do I look forward to the release of this medication, which I predict will be released? I've never had one patient come to my office taking both

GLP-1 and insulin thus far.

I do think GLP-1s are an excellent medication for diabetics. I see patients coming with metformin, DPP-4 -- which I do not think a DPP-4 -- I think you all know what a DPP-4 is. Anyway, it's not as good as a GLP-1. They used to come in with metformin, DDP-4, and insulin. So in this way, we can have the primary care doctor start using the GLP-1s, which they seem to not use.

Again, I'm impressed by the lower dose of insulin and the decrease in hypoglycemia. It's my best medical opinion that, in those who today will use 70 units of insulin or less, this medicine is not for everybody. It's just for people who need about 70 units of insulin or less. If you're extremely insulin-resistant, this medicine is not going to be very good for you.

But the majority of people who would use 70 units of insulin or less will do very well with metformin, IDegLira, and an SGPT-2. I think, with that regimen, I would say 90 percent of people would have hemoglobin A1c's less than 7, even a

very great percentage having under 6.5.

But again, the most compelling reason for the approval of this medication is that it works. Thank you very much.

DR. SMITH: Thank you. Will speaker number 7 now please step up to the podium and identify yourself? Please state your name and any organization you are representing for the record.

DR. JOHNSON: Certainly. Thank you for the opportunity to address this committee. My name is Dr. Nicole Johnson. I am a patient. I'm a public health professional, and I had the great fortune of being named Miss America 1999 with type 1 diabetes.

Today, I'm here because of my professional connection to diabetes, working in an academic research setting. In my participation today, the diaTribe Foundation generously helped provide for my travel support.

So as a public health professional, my greatest concern right now in the diabetes population is the risk and the growing breadth of the condition, especially in the newer category of

pre-diabetes, which tends to be the category that I work the most in at this point in time.

The combination drug being addressed today holds so much promise for so many different people in the diabetes community and that's been evidenced by the research data.

For the group of individuals with type 2 diabetes and even potentially others in other categories of the disease, it's exciting to provide a solution that could aid a population of individuals who feel helpless, who have often been told that they are in a poor state of health, who are disempowered, and who feel worried about their futures. It would be a gift.

This population is often intimidated by or scared of initiating the use of diabetes products, especially when confronted with the opportunity of multiple products.

The combined element of the drug that you're talking about today, though, makes treatment of the disease less confusing and less intimidating for most.

It creates a safety element for those who could misdiagnose or confuse multiple products that are in their medicine cabinet or refrigerator.

The evidence of this drug's utility in weight management is particularly exciting. We know that modest weight loss of 5 to 7 percent can have incredible benefits, including halting the progression of diabetes whether you're in a prediabetes state or with type 2 diabetes.

This is the recommendation; this is the element that could be most exciting for patients. The lower weight gain or the weight loss element is a motivator that will reverberate from patients throughout the various sectors of life with this disease.

That promise of improved health and thus lower risk will improve their quality of life. This combination drug could be part of the solution, at least in my view, in turning the tide of the frightening trends that we see in diabetes generally.

This is what excites me so much. As a

public health professional, I teach diabetes classes, I train trainers who teach diabetes classes, and, thus, I witness firsthand the fear that exists both in patients and in professionals as they consider options for their patients.

As the daughter of an individual with type 2 diabetes, I also witness in a family setting the incredible frustrations that exists. Watching a loved one struggle with decisions about diabetes medication and the challenges associated, watching them confront fears about changing habits, about their life, about their longevity is something that is difficult.

This type of medication could help improve my father's quality of life. And on a personal note, as an individual with type 1 diabetes, I have used GLP hormone products for years and have seen incredible benefits.

The freedom, the psychological freedom that accompanies these personal victories of feeling stronger, of feeling more in control and of having a higher quality of life give me the motivation to

continue on a daily basis.

So thank you for your consideration of these comments.

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 may be representing for the record.

MS. KOFMAN: Hi. My name is Nicole Kofman from the diaTribe Foundation and today, I'm speaking on behalf of Joyce Gresko, who is unable to here today to read her prepared written statement. She has no financial disclosures to share.

"My name is Joyce Gresko and I'm here to urge the committee to recommend approval of Xultophy for use in the U.S.

"I am a healthcare attorney here in Washington and I also am someone who has had diabetes for more than 25 years, to date without complications, which I think makes me an expert in what it takes for patients with diabetes to be

successful.

"It requires safe and effective therapies, adherence by a patient to a treatment plan and meaningful access to a wide range of therapeutic options. I believe that Xultophy is a drug product that will go a long way towards meeting all of those needs for many patients.

"First, Xultophy has been shown to be incredibly effective in reducing A1c's in patients who already are being treated with some kind of insulin therapy.

"It has been shown to lower A1c's in these patients by almost 2 percent, a remarkable result. And the reduction in A1c was greater for this combination product than for each of its component products.

"The UK Prospective Diabetes study and other subsequent studies have shown that lowering A1c's and those with type 2 diabetes correlates positively with reduced microvascular complications.

"Importantly, Xultophy already has been

shown to be safe in patients who are properly instructed in its use. And trials showed fewer hypoglycemic events compared to basal insulin alone.

"Xultophy would be a positive contribution to the toolbox of therapeutic agents that can help type 2 patients lower their A1c's, resulting in fewer complications and better outcomes for patients.

"Second, for patients who would benefit from combination of basal insulin and a GLP-1 agonist, Xultophy would promote adherence to prescribed drug therapy.

"Simply put, taking one injection is less work than taking two injections. And the drug does not have to be taken at mealtime. Even for those who may be accustomed to sticking themselves with needles and lancets, fewer pokes is better.

"One combination injection would also decrease the chances that a patient would forget to take one drug or the other. Even the most dedicated patients are busy and distracted in their

real lives so anything that facilitates adherence to a treatment plan is a step in the right direction.

"The evidence showing lower rates of hypoglycemia and reduced weight gain compared to basal insulin alone are also likely to encourage patients to stick with a plan that includes Xultophy.

"FDA's approval of Xultophy would also provide patients in the U.S. with access to another safe and effective drug therapy. But that would be just one step towards providing access.

"Access also involves inclusion in drug formularies and affordability for consumers. While I can't speak to the eventual price in the U.S. for this drug, I can say that one copayment for Xultophy is better for patients than two separate copayments for a basal insulin and a GLP-1 agonist.

"Like any other drug therapy, Xultophy may not be optimal for every patient. But for those patients whose treating clinicians feel that Xultophy would be effective for lowering A1c's with

no or minimal side effects, it should be available in the U.S. as it is in much of Europe currently.

"I urge the advisory committee to recommend approval of Xultophy for use in the U.S. Thank you for your consideration of my comments."

DR. SMITH: Thank you. Will speaker number 9 please come to the podium and introduce yourself? Please state your name and any organization you may be representing for the record.

MR. EDELMAN: Hello. My name is Steve Edelman and I am not only a person living with diabetes for the past 47 years, but I'm also an endocrinologist at the University of California, San Diego and Veteran Affairs Medical Center, where I'm involved in teaching clinical research and patient care.

I'm also the founder and director of a national not-for-profit patient-oriented organization called Taking Control of Your Diabetes.

Although I wear many different hats, I'm

here today primarily as a physician who sees numerous patients with type 2 diabetes in clinic and at our conferences around the country.

I have come here on my own time and expense and my comments are my own. I do consult for several pharmaceutical and device companies in the diabetes space, including both Novo Nordisk and Sanofi.

My interest today is solely improving diabetes care and my comments are pertinent to both GLP-1 receptor agonist/basal insulin combination products presented here today, as well as tomorrow.

Despite the plethora of new oral and injectable agents, including insulin and GLP-1s, glycemic control has not significantly improved in this country during the last 10 years.

According to the NHANES, Medicaid, and largely commercially-insured databases, the A1c has remained flat. In fact, the number of people with an A1c over 9 percent has actually increased. Now, there is something seriously wrong with this picture.

Now, there are many reasons that may explain this phenomenon, but patient adherence is a major one. Administrative claim and PBN [ph] refill data consistently show that adherence and persistence with type 2 diabetes medications is shockingly poor. And this is especially true with injectables.

Because of the asymptomatic nature of poorly controlled diabetes, there is a limited sense of urgency. And any therapy that is effective, safe, and easy to administer will help with adherence. And improving adherence is really where the rubber meets the road in clinical practice.

No diabetes product will make up for the common problems we see in our healthcare system like lack of face time when we're seeing patients or reduced access to appropriate medications.

However, these combination products are made up of two different classes of agents that have been around for a long time and quite frankly have withstood the test of time in terms of safety. And the potential to improve diabetes care at the

community level is impressive.

I realize that the exact dose of either the GLP-1 and/or basal insulin may not be right for all patients, but having this option in our toolbox will be greatly beneficial.

Now, in addition, treating multiple defects of glucose homeostasis in type 2 diabetes is often needed, in most cases, to get patients to goal. This combination of a GLP-1 and basal insulin is by far the most potent yet safe and easy-to-administer class of agents that we've seen in clinic in a long time.

Living with type 2 diabetes is tough and successfully treating this condition, which includes hypertension, dyslipidemia, and obesity is extremely challenging.

So on behalf of people with type 2 diabetes that are willing to accept the risk-benefit ratio of these products and healthcare professionals who take care of these patients, I would hope that this panel and the FDA seriously consider their approval. Thank you very much.

DR. SMITH: Thank you. Will speaker number 10 now please step up to the podium and identify yourself? Please state your name and any organization you may be representing.

MR. COHEN: My name is Brian Cohen. I'm here as a private citizen. I have no financial ties. I was diagnosed with type 2 diabetes 11 years ago. I wish to speak to you today about my experiences as patient with the effectiveness and quality of life associated with GLP-1 drugs and insulin use.

As my diabetes progressed, I cycled through essentially all the available type 2 medications, including Byetta and Victoza. The GLP-1 drugs really helped my blood glucose response to meals. But I still suffered from constantly high fasting blood sugars. And at the time, there were literally no type 2 medications that would help my fasting blood sugars.

So the obvious course was to start a basal insulin. And at the time, I really didn't have an option to combine a GLP-1 with a basal insulin.

Byetta was approved as a separate add-on to Lantus only in 2011.

Instead, I was faced with a very difficult decision, kind of a wall in my journey of treatment. I had to move to a full insulin regime, taking 4 to 5 insulin injections a day, counting my carbs, and moving instantly to being fully insulin-dependent on both the basal insulin and a mealtime insulin.

I would dearly have liked at that time to have had the option of combining a GLP-1 like a Victoza and a basal insulin like Tresiba that would enable me to take one daily injection and have one co-pay.

The Victoza would have controlled by blood sugars for meals without having to worry about closely counting my carbs and taking on the risks of dosing a bolus insulin, which could very easily go wrong. And then the Tresiba would have finally controlled by fasting blood sugars.

I have to say many patients, as has been mentioned before, fear insulin. They associate it

with a failure in their treatment and that it basically is the end of their road as a patient.

It can also be very difficult to learn to use properly. It's hard to take insulin for each meal, and do it right, and avoid hypos and high blood sugars. The ability of any patient to properly implement an insulin regime is nowhere near 100 percent, even for someone who's very experienced at it.

I would also note that the decision to move to insulin for a patient involves accepting a certain amount of risk and they have to be part of the conversation with their doctor. I would point out that it's not just the patient who has difficulties with moving to insulin. It's also difficult for doctors. I found my doctors actually were extremely insulin-resistant.

In my path, I was actually told that I would only be prescribed insulin as a last resort. In my case, I'm a proactive patient. I asked for insulin for over two years before finally giving up hope that my doctors would grant me insulin. So I went

to Walmart, and I bought insulin over the counter. Few patients would do this. I made this decision to accept the risk. I want to be part of the conversation with my doctor and part of the conversation with you here at the FDA.

So in summary, as a type 2 patient, I would encourage you to consider how this simplified treatment regime, using a combination of Victoza and Tresiba, may really improve the effectiveness of the treatment regimes.

It may significantly reduce the hurdle that patients face when moving from type 2 medications to insulin and, overall, that quality of life improvement may significantly improve the patient burden and cost, as well as improving patient adherence to treatments. Thank you.

DR. SMITH: Thank you. Will speaker number 11 now please step up to the podium and introduce yourself? Please state your name and any organization you may be representing for the record.

MS. RUNGE: Good afternoon, everyone, and

thank you for the opportunity to speak. My name is Ava Runge and today, I'll be representing dQ&A, a diabetes market research company based in San Francisco. As far as disclosures go, I also work for Close Concerns, who paid for my flight here today.

On a personal note, I've had type 1 diabetes for almost six years, which has given me some firsthand experience into the challenges of managing diabetes on a daily basis with insulin therapy.

So today, I'd like to use some survey data from thousands of patients with diabetes to compare Xultophy to one of the more challenging transitions of diabetes therapy, the intensification of basal insulin to multiple daily injections.

This is a critical step for many patients as their diabetes progresses. However, patients often delay this intensification 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 all patients

on basal insulin have talked to their doctors about adding meal time insulin.

This percentage was low even for those with an A1c over 9 percent and only 22 percent of those patients have had this conversation with their doctor. So this is really troubling given the fact that delaying intensification in patients with an A1c this high can really raise the risk of disabling and costly complications.

dQ&A also asked patients, diabetes educators, and physicians about patients' biggest concerns about adding meal time insulin to their current basal insulin therapy. The top five responses were: It'll be more of a hassle; difficulty dosing insulin and calculating carbs; extra cost; increased hypo risk; and gaining weight.

Xultophy can address all of these concerns and that makes it an excellent alternative for millions of type 2 patients who require insulin intensification. Here's how.

In contrast to multiple daily injections,

Xultophy does not increase the hassle for patients on basal insulin as they will still only need to carry one pen, take a single injection, and fill one prescription. It also won't require carb counting for dosing and will only require a single co-pay instead of the two co-pays that patients have with basal and bolus insulin. And as we've heard today, Xultophy has a lower risk of hypo and weight gain compared to basal insulin alone.

So in summary, I think it's safe to say that Xultophy can be a real game-changer for type 2 diabetes management. Because it addresses so many of these barriers to optimal care, it can dramatically improve adherence, which will translate to better outcomes and a lower risk of complications.

This is a big win in terms of cost savings for the healthcare system and it's also a big win for patients. Ultimately, people with diabetes are people before anything else and that means they're juggling a million different things just like all of us that compete with their diabetes for time,

money and energy.

Xultophy can help lessen the burden of diabetes by making it easier to fit management into daily life. It's not every day that we have a chance to offer patients with therapy like this that can both improve their health and quality of life.

So I hope that, today, the FDA takes this opportunity to approve Xultophy and advance the health of millions of Americans with diabetes. Thank you.

DR. SMITH: Thank you. Will speaker number 12 now please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. REGIER: Good afternoon. Thank you so much for the opportunity to speak here today. 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 approximately 50 scientific and

regulatory meetings each year and speak frequently with a wide range of leaders in the diabetes field.

On a personal note, I'm also here as an aspiring physician who is eager to continue learning as much as I can about the latest research and advances in this field.

As far as disclosures go, almost 300 for-profit and non-profit organizations subscribe to our fee-based newsletter, Closer Look, including today's sponsor.

GLP-1 agonists and basal insulin combinations have been a frequent topic of discussion on the diabetes conference circuit over the past few years.

I hope to convey here some of the excitement that these drugs have generated in the field. By my rough count, we've reported on about 50 talks at 17 different scientific meetings over the past three years that have been at least partially focused on these drugs.

This includes presentations on some of the most compelling data we've seen for any type 2

diabetes drug over the past few years. As we heard this morning, IDegLira beat both of its components in phase 3 trials in terms of A1c reductions, allowing about 80 percent of participants to achieve an A1c target of less than 7 percent.

Other trials have shown that switching to IDegLira produces greater A1c reductions than continuing treatment with insulin glargine, a GLP-1 agonist, or oral diabetes drugs.

Perhaps even more importantly for patients, these improvements come with less hypoglycemia and weight gain compared to basal insulin alone, less nausea compared to a GLP-1 agonist alone, and only one injection instead of the two that will be required to use both components separately.

It's also clear that key opinion leaders see these drugs as extremely versatile. We've heard them described as the modern equivalent to basal plus therapy, a superior alternative to basal insulin or liraglutide, logical to use early in the disease progression, and potentially even the best drug to use after metformin. Dr. John Buse once

went so far as to say that it would be hard to identify a population ill-suited to treatment with these combinations for clinical reasons.

So while IDegLira or other combinations will obviously not be the right choice for every single person with type 2 diabetes, it does seem like it will be an appealing option for an unusually diverse range of people.

I want to close with just a few additional testimonials from speakers on the conference circuit to reinforce the excitement we've been hearing about these combinations.

These combinations hold great promise, more than the sum of their parts in terms of efficacy, tolerability, safety and quality of life. Most of the literature now says this is the ideal combination, the most effective way to treatment type 2 diabetes, bar none. If I only get one shot on goal, I do think this is the single best shot we have, no pun intended.

So I encourage the advisory committee to consider these opinions when making your decision

today. Thank you so much for the opportunity to speak.

DR. SMITH: Thank you.

So now, speaker number 13, would we please step up to the podium and introduce yourself? Please state your name and any organizations you may be representing.

MR. HERRING: Good day, everyone. My name is Douglas Herring. I'm 40 years old. I'm from Fresno, California. I'm a patient of Dr. Paul Norwood of Valley Research study. Novo Nordisk has paid for my travel to attend this meeting and I'm not receiving any additional compensation.

I was first diagnosed 10 years ago when I got a staph infection in my left ankle. I went to the emergency room. The infection was not healing and they referred me to a local podiatrist. The podiatrist saw signs of diabetes and referred me to a doctor, who then tested me for diabetes.

It was at this time I was diagnosed with type 2 diabetes. I don't believe the doctor was

very knowledgeable because he said that my diabetes could be managed with diet and he wasn't too concerned because I was only 30 years old.

Diabetes runs in my family as my father has it as well. He was taking pills and well controlled and paid close attention to what he ate. At about this time, my best friend was diagnosed with diabetes; he was 28 years old.

I started to realize how common diabetes was. For the next few years, I didn't take such great care of myself. I was still eating an unhealthy diet and drinking beer. It really had a negative effect on me. I was falling asleep within 30 minutes of eating and my blood sugar was always very high.

My girlfriend said I needed to do something about it, so she made an appointment for me with the Valley Research Center. In late October of 2011, I was diagnosed with insulin-dependent type 2 diabetes.

My study coordinator, Lucas Anderson, placed me on Lantus and 800-milligram metformin. I

started to feel better once I was on medication, but for the next three years, I was unable to lower my blood sugar below 150 on a daily basis, even with diet and exercise.

In late 2014, Lucas Anderson, my study coordinator at Dr. Paul Norwood's office of Valley Research, called me and asked me if I wanted to participate in a clinical trial for a new combination mixture of Tresiba and Victoza.

At the beginning of the trial, my blood sugar average was 175-195. One of the biggest difficulties for me while dieting was to give up sugar, starch, and beer.

While being in this study, I learned about foods that create lots of sugar in the body. After two months, I was finally able to give up the sugar, the beer, cutting them out completely. I also cut out my bread in-take to three days a week. My cravings went away while I was on the new medication.

I work as a tow truck driver and I sit 9 to 12 hours per day, so exercise is very important to

me. Because the medication was giving me more energy, I started exercising two hours a day, four to five times a week. I notice a difference in my weight and my ability to stay more focused on and off the job.

The best thing about this medication was I lost 60 pounds and 3 inches off my waist. The medication also lowered my daily blood sugar from 120 to 150, lowering my A1c from 9.5 percent to 5.5 percent.

My family noticed the change in me. I had more energy in my body to do more things in my daily life, both at home and on the job. I didn't know that diabetes was having such an impact on me until I started to feel so much better.

While in the study, I reached the max dose of 50 units of insulin in a 26-week period. Since the study ended, I have gained 30 pounds of my lost weight and added an inch back to my waist.

I still do not have the cravings for high sugar and beer. I'm still exercising and would say I feel great but not as good as I felt during the

trial.

I believe if this medication was available on the market doctors could prescribe, it would benefit a lot of other diabetics like myself who are insulin-dependent and help them lose weight, maintain the energy and give them life back to a healthy level. Thank you for your time.

DR. SMITH: Thank you. So now, will speaker number 14 please step up to the microphone --

DR. NORWOOD: I want to just make a point. My coordinator gave him insulin under my direction.

DR. SMITH: Okay. Thank you.

DR. NORWOOD: Okay.

DR. SMITH: Would speaker 14 please step up to podium and introduce yourself? Please state your name and any organization you may be representing for the record.

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, five years ago, I ended my involvement in the clinical trials of both IDegLira and exenatide and glargine.

Although the American Diabetes Association does not testify in support of any individual products, we strongly support the need for further research in the improved therapies for the treatment of diabetes as an unmet need.

The American Diabetes Association has been annually revising and publishing the standards of medical care for diabetes. And many of the speakers today have been citing our findings in this evidence-based clinical practice.

We are internationally recognized as the gold standard with every recommendation having an evidence level. These standards emphasize the importance of a patient-centered approach to therapeutics in which choice, flexibility, and individualization are pivotal.

We recognize that one size definitely does not fit all. In 2015, we introduced the combination of basal insulin and GLP-1 receptor

agonists as a therapeutic option in the treatment of type 2 diabetes with level A evidence.

Type 2 diabetes follows a progressive course as demonstrated in both the United Kingdom Prospective Diabetes study and in the ADOPT trial. Historically, clinical therapeutics has proceeded on a treat-to-failure paradigm in which a single med is administered until it fails and then another med is added.

Clinical inertia or delays in medication adjustment have been documented in multiple populations leading to prolonged exposure to hyperglycemia. Given the multiple contributing factors to the development of type 2 diabetes, there's a convincing argument that a combination of medications with different mechanisms of action should be used earlier in the course of the disease as opposed to waiting for treatment failure as is currently done.

Early aggressive intervention had demonstrated long-term benefit in the development of both micro and macrovascular complications.

Thus, earlier initiation of combination therapy with treatment-to-goal, as opposed to treatment-to-failure, avoids the conundrum of clinical inertia. However, combination therapies need to minimize side effects of the contributing components. This can be accomplished by the observed dose sparing effect seen with these combination therapies.

One may ask, why is there a need for a fixed-dose combination if both components are available and approved? Let me ask the committee members to consider their own behavior.

Are you more compliant with pills you have to take once a day compared to multiple pills per day? The literature is clear that treatment adherence is considerably better with a simpler treatment protocol. Medication is ineffective if it never leaves the bottle.

Now, consider that we're dealing with two injectable medications and that these drugs are used for a lifetime and one sees that a fixed-dose combination would save 3,650 injections per person

over a 10-year period of time.

Adherence is also a function of cost. Using basal insulin and GLP-1 receptor agonist as separate preparations, as others have said, will require two co-pays for the patients as compared to a single co-pay for the fixed-dose preparation. Medication is in effective if it's never purchased from the pharmacy.

Finally, it's critical to keep in mind the differential clinical needs of people with diabetes. One size does not fit all. Clinical judgment calls for matching therapeutics to the clinical goals of the person with diabetes.

Shared decision-making, appropriate therapeutic options, and choice are prerequisites to achieving the stated goals of personalized or patient-centered medical care. Thank you.

Clarifying Questions (continued)

DR. SMITH: Thank you. And thank you to all of the open public hearing speakers.

The open public hearing portion of this meeting has now concluded and we'll 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 we get to the discussion questions posed by the FDA, I'd like to take some more time as we needed for further questions related to clarification from both the FDA and from the sponsor. Perhaps we could start with the questions from this morning that required a little work to try to pull some data together.

DR. GOUGH: Thank you very much. There were a number of questions and comments raised this morning and we are asked if we could pull some slides together or pull some data together to address some of those concerns. And we have been able to do that.

The first main topic were the concerns in relation to titration and the end-of-trial A1c. And I think it's really important for me to emphasize that it's glucose stability and not the insulin dose that determines the final A1c and

makes that A1c reading valuable.

We know that insulin doses do change and they change progressively with time. And this isn't just to achieve target, but it's also to maintain target.

If I show you some data from Trial 3697, so what I'm showing you here on this slide from Trial 3697, if you remember, this was our 6-month study that was extended to 12 months. I'm showing you here the mean number of dose adjustments, a cumulative function over 12 months.

The important points on this slide are that, in the first two months, you see the number of dose adjustments for IDegLira and insulin degludec are very similar during the period of time where we're trying to achieve a fasting glucose target.

But then the lines diverge and you can see there's actually more adjustments, not less. There are more adjustments to insulin degludec and this, as I'll show you later, is to help maintain the fasting glucose values, not achieve further reductions in glucose values.

You also asked us if we could provide some data on why patients do not titrate when they're not at target. And what we have here are some data for IDegLira and also for insulin degludec. And quite simply, in Trial 3697, the main reason that patients did not titrate IDegLira was because they'd reached their maximum dose.

The main reason, the main single reason, that patients did not titrate in the insulin degludec dose are hypoglycemia or a fear of hypoglycemia. So I think that was one of the questions that we were also asked.

This slide goes back to the point that I was just making about having to increase the insulin dose to maintain the fasting glucose level. And again, what you can see here for 3697, over the 12-month period, is similar proportions of patients achieving their target A1c over the first few weeks.

But then when we get to around 12 to 14 weeks, we then start to see this period of stability where, although there are more patients

at target with degludec, the IDegLira and degludec proportion of patients at target, there's a constant -- the difference remains constant between them.

This then takes me on to the next slide, which further demonstrates the point that I'm making about increasing the insulin dose. We're not seeing any further reductions in the mean fasting glucose.

The major reduction in fasting glucose is in the first 8 to 12 weeks. And then we see a period of stability in both the IDegLira and insulin degludec arm. And that stability is maintained from 12 weeks to 26 weeks when we do our end-of-trial A1c.

Then you can see over the 52-week extension there's no further reduction in the fasting glucose and the A1c's are completely flat. That's despite the fact that the insulin dose is increasing and confirming that the increase insulin dose is to maintain the blood glucose level.

I think there was also a concern raised with

the 12-month data because of missing data. We actually did have quite a high completion rate at the end of 52 weeks, and we've also done a sensitivity analysis for the change in A1c, not just at 6 months but this is at the end of 12 months. You can see here that the different sensitivity analyses support the primarily analysis, suggesting that that primarily analysis is robust.

From a clinical perspective, I would just like to ask Dr. Sorli to maybe explain the clinical relevance of what he sees this in normal clinical practice.

DR. SORLI: Thanks. The clinical use of basal insulin and particularly the titration of basal insulin in clinical use is extremely relevant for this discussion.

When basal insulin is part of my treatment regime, my goal is to get patients to a glycemic level that is their target and do it safely. The tool I will use for basal insulin is the fasting self-monitored plasma glucose.

In fact, my goal is not to maintain or achieve a maintenance dose of basal insulin. I tell patients every day, the worst thing that I can tell you is this is your basal insulin dose. And part of that is because diabetes is a progressive disease.

I know, in someone on basal insulin and oral agents over time, their basal insulin dose will continue to gradually increase to achieve my goals. In fact, it's one of the things we deal with clinically when we start to get to a point where we're worried about over-basalizing people and subjecting them to the risks of hypoglycemia and further weight gain.

So really important to understand, the tool is fasting glucose, but the ultimate clinical parameter is going to be A1c target, do it safely. And it's never going to have a stable maintenance insulin dose. Thanks.

DR. SMITH: So do any of the panelists who had questions on this point want to follow up? You don't have to.

(No response.)

DR. SMITH: Okay.

DR. GOUGH: The further question we had was in relation to the proportion of patients achieving the maximum dose of 50 of IDegLira, and I said that I would pull that for each of the studies.

So what we have here is actually the distribution of patients by end-of-trial dose for each of the studies. You can see here on the left-hand side of the slide, we have two trials for patients on oral antidiabetic agents.

In Trial 3697, which was our largest pivotal trial, around 40 percent of patients got to the maximum dose of 50 of IDegLira. In Trial 3951, it was around 12 percent. A higher proportion in Trial 3912, just over 60 percent, got to the maximum dose of 50.

I have to point out, I think this was a function of the trial design where were driving patients to that higher dose. But then, if you look at Trial 3952 and Trial 3851, you can see between 40 and 50 percent of patients get to that

maximum dose of 50 of IDegLira.

Importantly, in that final category in each of the studies, between 60 and 70 percent of patients achieve a target A1c of 7 percent even though they're at the maximum dose.

A further question related to this was built on, I think, one of the earlier questions we had in response to our presentation. But you asked me about baseline clinical characteristics in relation to patients achieving that maximum dose. So I showed some similar data this morning, but this is now for Trial 3912 and 3952.

I'm showing you the patients. There's a number of columns here but, with respect to 3952, you can see we've split this up into patients at less than 50 and patients at 50 and similarly for Trial 3952.

Again, you can look across the lines and you can see that there are some small differences between the different clinical parameters. We touched upon body mass index, weight and body mass index, this morning.

So there are some small differences between those that get to a maximum dose of 50 and those that don't, but nothing that we could use to predict who would get to the maximum dose and those that would not.

There were then some questions related to safety and I'll call upon Dr. Hobbs to take you through those data.

DR. HOBBS: Thank you. I think I can answer the two questions on safety rather quickly.

First and foremost, around renal function, it's important to remember that in the liraglutide or the degludec program, in neither program did we see or identify a worsening of renal function in that program. And also, we have not seen that in this program.

Specifically, there were around 40 percent of the patients came in with mild renal impairment and around 6 percent with moderate renal impairment. Then if you would look just briefly at overall AEs, the patterns and the rates were very similar between the different definitions of renal

function, so no difference there.

Then also looking at specifically GFR track throughout the time course of the trials, those three, again, confirmed there wasn't a worsening of renal function seen with IDegLira. The other question was centered around the GI adverse events and were there any specific nature to inflammatory conditions.

What we are able to do is taking the GI adverse events and looking at the high-level group term of gastrointestinal inflammatory conditions. Remember that there is a 3:1 randomization versus GLP-1 and roughly 2:1 versus basal insulin.

You do have sort of a long list of single or different AEs there with no real difference or significant difference in those percent that are reporting one or the other.

For GLP-1, there's been no post-marketing signal in the way of inflammatory GI conditions. And we certainly would monitor this closely in any future trials if it was a concern.

Dr. Smith, did that answer your question?

Okay.

DR. GOUGH: Thank you. I think they were all the questions that you asked.

DR. SMITH: Yes. Thank you. Thanks very much.

So I'd like to follow up now on any further clarifying questions that members of the panel may have. There were some people that had questions earlier in the day and perhaps someone else asked the same questions in the interim. But we'll start with Dr. Cooke. You had a long-standing hand up this morning.

DR. COOKE: Thanks. I would like to ask the sponsor to directly address this question of glucose-lowering effect of liraglutide doses below that 1.2-milligram dose.

We've seen data that you've presented in these studies that suggest that that liraglutide dose was effective at lowering glucose across the whole range of the IDegLira dosage used. But we also heard that, in the trials of liraglutide prior to this, doses less than 1.2 were not effective at

lowering glucose.

So I'm interested in what your take and explanation for that difference is. Ideally, I'd be interested to hear were there earlier trials that used liraglutide with insulin that specifically didn't see effects at those lower doses?

DR. GOUGH: Thank you. I think the data here, with respect to liraglutide, are quite consistent and that, if I show you, what I have here is a dose response curve for liraglutide.

This is taken from two phase 2 studies in people with type 2 diabetes. And these curves were generated from two studies where the lowest dose is 0.045 milligrams of liraglutide, going up to a maximum dose of 1.9 milligrams.

The circles and the squares represent absolute data points and the curves are modeled on those data points. And what we've plotted here is the change from baseline A1c against the liraglutide dose.

If I then draw your attention to the

right-hand side of the slide, in the box, from these curves, what we can show you are the model estimates for the change in A1c. So you could see here, if we have an IDegLira dose of 10, which would be equivalent to a liraglutide dose of 0.36 milligrams, then I'd take you across to the change, the model estimate change in A1c, you can see we would expect a change in A1c.

This is for liraglutide monotherapy. It's clearly showing effect at these lower doses. It's not the maximal glycemic response that you see when you use liraglutide on its own and for which we had to achieve levels to achieve our license and to achieve to satisfy regulatory guidance. But it is having an effect at these low doses.

Remember, with IDegLira, it's a combination in which we're using insulin as well. So I think these data do support an effect at low doses.

DR. SMITH: Dr. Meisel, did you have a question? Yes?

DR. MEISEL: A quick follow-up on that, would you then consider applying for approval for

lower doses of Victoza on its own?

DR. GOUGH: But I think that's a completely different question.

DR. MEISEL: I know.

DR. GOUGH: The important thing with these lower doses that we see with IDegLira is when liraglutide is being used in combination with insulin, it's a combination product. I wouldn't like to speculate on the clinical effectiveness using it alone. What I'm talking about here is using it in combination with insulin.

DR. EVERETT: Just a quick clarifying question on that last slide, was that liraglutide or was that the combination?

DR. GOUGH: Sorry if I didn't make that clear. That was liraglutide, and this was from the phase 2 -- these were two studies from the phase 2 -- there were two phase 2 studies from the liraglutide development program.

DR. EVERETT: Okay.

DR. GOUGH: So this is the liraglutide monotherapy.

DR. EVERETT: Okay. All right. So the little blue bit about liraglutide dose at the bottom?

DR. GOUGH: Sorry. That relates to the table. I'm sorry about the color-coding there. That relates to the table -- sorry about the color-coding. One of those --

DR. EVERETT: The changes in A1c that you've got in the table are imputed from the monotherapy?

DR. GOUGH: Yes.

DR. EVERETT: These are not phase 2 trials of the combination of the two drugs?

DR. GOUGH: No. This is a phase 2 trial of -- two phase 2 trials of liraglutide.

DR. SMITH: Dr. Neaton?

DR. YANOFF: Just an FDA follow-up on that before we move on, is that acceptable?

DR. SMITH: Yes.

DR. YANOFF: Thank you.

DR. KHURANA: Hi. My name is Manaj Khurana, Office of Clinical Pharmacology. So the dose response data that the applicant has shown is not

easy to translate directly, that information, in the setting of the combination administration. There are challenges. Dose-Response data, as it stands, stands only for the monotherapy, and we don't know how that will behave when we are talking about the combination.

DR. SMITH: Okay. Dr. Neaton?

DR. NEATON: Two questions, maybe the first for the FDA, so you made an argument. I thought the analyses were very nice in terms of that because of the titration and the maxed dose in one of the studies that, likely, the hemoglobin A1c differences could be overestimated.

But isn't it also true then that the hypoglycemia and weight change differences are also underestimated?

DR. YANOFF: The overestimation of A1c has more to do with the time frame of the study.

DR. NEATON: Well, part of it relates to the time frame. Part of it relates to the maxed dose, and so, I mean, it seems like kind of the balance of what you said is that there may be a greater

risk -- kind of it was more real life, for example.

DR. YANOFF: Right. So I gave that -- the time frame, we believe that the clinical effect may be not representative of clinical practice; the same with the other components of the effect of the drug could be not reflective, either under- or overestimated.

DR. NEATON: Okay. And the other question, maybe it's for you or the sponsor. I guess I'm puzzled --

DR. GUETTIER: I would just address this question a little more. Again, these trials are designed to look at HbA1c changes. They do collect weight and they do collect hypoglycemia mostly for a safety perspective. But I think, as was stated in the clinical presentation, if the sponsor were to come to us to ask for a claim of reduction in hypoglycemia, the design of these trials would look different.

The endpoints and the definitions that would be used for a hypoglycemic claim would be different. So I think, in the end, we don't really

know with the secondary endpoints would look like.

If you were to have used insulin in the way that it would be closer to practice, in theory, I think you're correct. If you're thinking that insulin doses, aggressiveness of use of insulin is linked to hypoglycemia and weight gain, I think you're correct.

But again, the magnitude of change that would have resulted or whether or not we would have seen anything different is something that we can't report.

DR. NEATON: I agree there's some speculation on both. I'm just trying to understand risk-benefit for the trials that we've seen. But the other question for the sponsor or the FDA is, I guess I'm surprised, given what is stated. Maybe I don't fully understand the multiple imputation.

Essentially, your point estimates for the difference, they almost line up identically. And I just wonder whether these methods are appropriately accounting for the fact that there was a differential time period of dropouts on the

different arms.

I mean, I haven't seen any data from either the sponsor or the FDA that actually considered when the withdrawals occurred. There were a couple of graphs that suggested the withdrawals were much more rapid on the control arms.

But was that taken into account when you did this multiple imputations? Were you actually considering post-randomization values in doing the multiple imputation and kind of taking into account when they occur differentially in the two arms?

MS. KETTERMANN: The imputations were done in two ways, the jump to reference approach and the copy to your control. So jump to reference uses all the values until the person dropped out.

DR. NEATON: So you used all the values -- you were imputing 26 weeks or were you imputing the full course of values over the follow-up period?

MS. KETTERMANN: In my analysis, I imputed all of them.

DR. NEATON: You imputed all of them. Okay.

All right.

MS. KETTERMANN: Someone might have it different.

DR. NEATON: And your results line up with the sponsor's?

MS. KETTERMANN: They were close.

DR. SMITH: Okay. So if there were no more -- Dr. Meisel?

DR. MEISEL: For the FDA, just a couple of quick questions, are you aware of any other product that's on the market that has two active ingredients but we refer to only one of the doses?

DR. GUETTIER: We'll call the DMEPA because they're the experts in that question.

DR. MERCHANT: My name is Lubna Merchant, and I'm from the Division of Medication Error Prevention and Analysis.

So we did look at the range of products that are out there which are multi-ingredient and have different units of measure or measure terms. But we don't have any products out there that essentially are dosed using just one unit of

measure.

So in general, if you have other products out there which have different units of measure, they are basically ordered in terms of either one tablet or one application.

The dosage is in terms of a standard unit. So even if the individual components are dosed using different measure terms, the dosage translates into a standard unit of measure like a tablet or something like that. This is unique in the sense that both ingredients are titrated.

DR. MEISEL: I have a very related question. My understanding is that the suggestion is not to use term "units" with this because that would be deceptive. We would just use the word "10," or "15," or "20" or something.

Are we aware of any other products on the market that have no unit of measure designation associated with it?

DR. MERCHANT: Again, we are not aware of any other product on the market that has no unit of measure associated with it.

As I mentioned before, if the individual components are not used in the dosage, then it's translated in the term of standard measure like a tablet or XXML, so on and so forth.

DR. SMITH: Dr. Stanley?

DR. STANLEY: This is a question for the sponsor. I was trying to get a handle on the distribution of doses and patients. I gather about 25 or 30 percent of patients are being dosed at a level that's below the equivalent of 1.2 milligrams of the liraglutide, but that about 40 or 50 percent of the patients by the end of the titration are up at 50 units of the combination.

Since you said that doses' requirement for insulin over time are going to go up, that means that essentially, within several months, those patients are going to no longer be under control. They're going to have to switch off.

Can you interpret that data for me?

DR. GOUGH: One of the things that we've seen with IDegLira -- and I can show this best in Trial 3697 -- is actually the A1c. And I admit, I

only have 12-month data here. But over the 12-month period, there's no shift in the A1c. So the A1c that we saw at 6 months at 6.4 is identical A1c at 12 months at 6.4.

I don't have a full explanation for this, but it is implying that IDegLira is maintaining stability or stable glycemic control over that period of time. What it would be like after 12 months is difficult to say. But certainly, over 12 months, we have this period of stability.

DR. SMITH: Yes, Dr. Everett?

DR. EVERETT: One possible explanation is that the people who don't have good glucose control dropped after 6 months when the trial ends, right?

DR. GOUGH: I can show you the characteristics of patients at 6 months, under 12 months and I can show you the dropout rates. And the dropout rates were actually extremely small over that 12-month period. But I accept that is a possible explanation.

DR. SMITH: Okay. So if there are no more clarifying questions -- Dr. Wilson?

DR. WILSON: So there has been some mention in the literature about these drugs where the GLP mechanism is no longer really keeping weight down after 12 months. Do you have 12-month data?

DR. GOUGH: The 12-month weight data for Trial 3697, I can show you. So this is Trial 3697. You can see the weight at 6 months and the weight at 12 months remaining stable in the IDegLira arm, which is the blue arm.

DR. WILSON: Yes. And then to follow up on that, where it's been used worldwide, do you have two-year data at all?

DR. GOUGH: I don't have any further data --

DR. WILSON: Not related to this application, but it has some relevance for what might be said in a product insert, et cetera because that is -- as was mentioned by many of the speakers, this is of special interest to people who take these products.

DR. GOUGH: I don't have post-marketing surveillance data with respect to weight.

DR. SMITH: Yes, Dr. Yanovski?

DR. YANOVSKI: In a similar vein regarding weight, it was said that there's about a 2-percent weight difference between people on basal insulin and people on IDegLira in terms of weight differential.

But mean weights don't tell the whole story and certainly, for obesity drugs, we're looking at categorical weight loss or weight gain. And it might be that there are certain responders, either people who have a lot of weight gain with insulin, people who have a lot of weight loss, 5 percent or more with IDegLira. And I wondered if you looked at weight change categorically in both groups.

DR. GOUGH: So again, what I can show you here across the trial program are those patients that lost more than 5 percent of their body for the IDegLira group versus the comparators.

I really draw your attention to the studies with basal insulin, so 3912 and 3952. Here, you can see that in Trial 3912, 27 percent of patients lost 5 percent or more of their body weight.

In 3952, which is IDegLira against an unrestricted dose of insulin glargine, you can see about 17 percent lost 5 percent or more of their body weight.

DR. YANOFF: Could you leave that on a little bit longer so he can confirm those numbers, please?

DR. GOUGH: Sorry.

DR. SMITH: Okay. Any more, Dr. Lesar?

DR. LESAR: Yes. I just have practical questions about potential labeling and instructions for prescribers and patients about what -- since the dosing titration is based on glucose, whether the instructions for patients who achieve their A1c targets but they don't have high glucose concentrations and vice versa, as well as obviously reading the instructions when you would hit that 50-unit cap.

DR. GOUGH: So with respect to our labeling, within our proposed label, we are providing the titration algorithm based on the 202 algorithm that we use in our clinical trial program.

That 202 algorithm should be used on an individualized basis by the clinician and the patients in front of them. So it's very much a clinician and patient decision on what the target is with respect to A1c and fasting glucose what to titrate based on the 202 algorithm.

DR. SMITH: Yes, Dr. Gelato?

DR. GELATO: So I just want to come back to this issue of the patients who were on insulin initially, and if I am assuming correctly, there was no one who were taken into your trials who are on more than 40 units of insulin, is that correct, at baseline?

DR. GOUGH: In Trial 3952 --

DR. GELATO: Or in any of your trials, they were?

DR. GOUGH: Yes, in Trial 3952, we recruited patients up to a maximum -- who were on a pre-trial dose of up to 50 units of basal insulin glargine.

DR. GELATO: Up to 50 units, okay.

DR. GOUGH: Yes.

DR. GELATO: And again, I'm just trying to

clarify in my own mind in terms of thinking about who would be a candidate for this. The amount of insulin that they were on when they came into the trial did not make a difference in how they responded to the combination therapy?

DR. GOUGH: It did make a small difference. I can try and pull some data to show you the end-of-trial IDegLira dose in relation to the pre-trial basal insulin dose. We do have those data.

It does make a difference in the extremes, but just a small difference --

DR. GELATO: Okay. So they weren't the patients who got to the 50 right away?

DR. GOUGH: No.

DR. GELATO: No. Okay.

DR. SMITH: Other questions?

(No response.)

Questions to the Committee and Discussion

DR. SMITH: Okay. So we're now going to proceed with the questions from the FDA to the committee and associated panel discussions.

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

So if we could proceed to discussion question 1, and I will read this. Discuss the benefits of starting the fixed-combination drug product containing liraglutide and insulin degludec 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 useful and address why you would select the fixed-combination product over use of an available GLP-1 agonist or basal insulin in these patients.

Explain your rationale using data from the briefing materials and presentations or from your own clinical experience.

Yes, Dr. Burman?

DR. BURMAN: Maybe I can start the discussion. And I appreciate the excellent

presentations of both the FDA and the sponsor and the very informative discussions from the patient advocates.

What I'm having trouble with is the issue of who exactly this medication be used on in an insulin-naïve patient. So for example, if a patient has a hemoglobin A1c of, let's say, 7 to 9 percent, why not just start with a single agent? Because if you start double agents, you may be giving them a medication that they don't need. And it costs money, and time, et cetera. And I realize the convenience of one injection however.

On the one hand, if the hemoglobin A1c is 9, or 10, or 11, I realize there are glucose toxicity issues. But most people are going to start as much insulin as they need and move up very rapidly with long-acting insulin probably with short-acting pre-meal insulin at the same time.

So I recognize the need in the physician armamentarium for this medication, but I don't have it clear in my own mind which group of patients it would be most useful for.

We don't have a study comparing the combination therapy versus individual independent agents to see which ones were more effective and got to the glycemic control quicker.

DR. SMITH: Thank you. Other comments on this point?

I've struggled with the same issue. Typically, in patient care, with concerns about side effects of drugs, which are often difficult to anticipate, it's wanting to expose patients to the minimum number of agents, i.e. one at a time, as one advances.

I understand that -- or I believe that there certainly are patients who benefit from both of these drugs. It's a question -- given simultaneously, the question is how to get there. And I had the same difficulty recognizing some of the advantages of using the drugs in combination such as potential effects in decreasing the weight gain that often occurs with insulin.

But I, again, feel confronted with the problem in anticipating how to start these on the

background of neither which is the variability in patient responses in terms of something such as weight gain. So certainly, for some patients, that's a major problem. It's difficult to predict that.

There are patients who are very resistant to taking insulin either because they have heard from various sources that weight gain is a problem -- and it can be very difficult to convince them otherwise -- or because perhaps they previously had a period of insulin treatment and they experienced weight gain.

So that might be a group of patients, perhaps not a very large one, where it really could make the difference in terms of persuading them to start insulin. That's the same group of patients, however, that one could alternatively potentially start on a GLP-1 receptor agonist.

I'm sort of carrying on, but if I had a patient who had pretty markedly elevated glucose levels, where I was anticipating that insulin would most likely be something that they would require

very strong probability, and I was in this situation of resistance, I can see situations where I might be able to convince that patient.

That patient might be comfortable accepting insulin knowing that they are getting a drug that will address a concern that -- that really for some patients, they simply won't take insulin no matter how terrible those blood glucose levels -- of course, I'm speaking from direct anecdotal personal experience.

So I guess that's one set of patients I can see where, perhaps not supported adequately by data, in terms of the anticipated response in that patient, in real life, it might make a difference in their willingness to accept insulin.

Dr. Wilson?

DR. WILSON: So I think it's helpful at this point to bring up the sponsor's slide or those who have a handout. They could look at CO-18.

This is the algorithm that's set forward by the American Diabetes Association and it's the starting point for those of us who are

endocrinologists. A tremendous amount of work has gone in to develop this over the last 20 years or more. And it's really targeted towards adults with type 2 diabetes.

If you'll look at the dual therapy, a line across virtually, most patients with mild elevations in A1c, all those options, the sulfonylureas, TZD, DPPs, SGLTs and the GLPs, are all applicable.

As Ken Burman was just saying, someone with a very high A1c -- and that's a qualitative number, but I think everybody would agree 10 plus is high -- would be going to insulin if they are seeing an endocrinologist rather soon. And you would, so to speak, put out the fire and then circle back to perhaps oral agents once that A1c is reduced to closer to 7s or 8s.

So the question is, of those five choices -- and this is a very complex slide. That's why I'm asking you to look at it. And it's shown at virtually every diabetes meeting for therapy.

Where would this new formulation fit? And for sure, one of the places it would fit is as a person who is a little lower, in the 7 to 8 range and would get a GLP-1 receptor antagonist, and if they do not get a good response right away, potentially you would get the combination therapy, because then, as you move to the triple therapy, you would go from an insulin to an insulin plus a GLP-1 drug. Now, the rationale could be do we have other combinations and that will be a discussion at other meetings.

But you can see it could become an ancillary pathway in association with a GLP-1 that's right there for people, I would say, in the high 7s to 9 plus A1c's, building exactly what Dr. Burman was talking about.

DR. SMITH: Dr. Berney?

MS. BERNEY: Thanks, but I'm not a doctor. I'm just a patient representative and I'm an artist. I also am diabetic, type 2. My mother was a type 2 diabetic. My father was on prednisone for myasthenia gravis for 20 years. He died from

diabetic complications. So it's throughout my whole family, grandparents.

I was called borderline for probably 20 years before I was diagnosed in 2002. I've been very lucky. I've been very compliant, and I managed to keep my A1c down to 5.7 for a long time. But I was diagnosed with myasthenia gravis in 2013, and the first line of defense didn't work. And I was put on prednisone for 2 and a half months.

But I also discovered, after a week or so -- my normal morning fasting read is 85 -- I was over 300 in a matter of a week or two. So I started on insulin. Within 2 and a half months, I had gained 30 pounds. I'm not skinny to start with. I'm generally really reasonable about my meds. I've got a lot of stuff wrong me; I take the medication I need.

But I rebelled. And I can tell you, from the patient's point of view, weight gain when you have diabetes or any of these other conditions where it matters is a huge thing, no pun intended.

After 2 and a half months, I just said to my

internist, I'm done, not doing this anymore. I quit the prednisone. The insulin continued to pile the pounds on. I quit the insulin and went back to just oral meds. I take a cocktail of Januvia, metformin, and glyburide. And within a very short time, I was back to my normal morning fasting reads. And within probably six months, I had lost all the weight.

So I can imagine that if you gain 3 pounds a year -- and I'm an artist; I don't do numbers, so kilograms, I can't do that conversation in my head. If you gain 3 pounds in 26 weeks or 2 pounds in 26 weeks and you're on this drug for the rest of your life, you could put on a considerable amount of weight.

So anything that would minimize that from the patient's point of view, plus the fact that I was having to give myself shots several times a day and remember to take my morning meds and my nighttime meds -- even as a really compliant, conscientious patient, I didn't get it right.

So I'm all in favor of things that make my

life simpler. And from the patient's point of view, I think most of us feel that way. So I just want to reinforce how important all of these other things are besides A1c because you can have a great A1c and be 200 pounds overweight. And that's not healthy either.

DR. SMITH: I appreciate that statement and it's sort of a confirmation of experience that I've had with a small number of patients in the extreme of actually stopping insulin because of concern about that and then technically being a patient not on insulin, as well as perhaps not on GLP-1.

Yes, Dr. Gelato?

DR. GELATO: I agree with Dr. Wilson that I think one of the places where this could fit is in people who have A1c's that are somewhere in that 7-9 range. I agree that, when you get to 10, you're really looking at having to treat the patient in a different way and I'm not sure this is the drug for that.

But I also think that I was looking at the data from the sponsor that there were a number of

patients who responded to relatively smaller doses of this drug. To me, that's a good thing because you're exposing them to less and getting them to their target. And I think that, say, for people who may be naïve to insulin or maybe have been on insulin, still, it looked like there was a fair number of patients who did respond well to the drug and never got to the 50.

So I think that even though it is two drugs, if you're giving lesser of both, then it looks like hopefully you might get them to their target and minimize any other effects. And if you mitigate the weight gain, which I agree with you is a real problem for patients, then to me, there's a place for this drug to fit in, in that category.

DR. SMITH: Dr. Kewalramani?

DR. KEWALRAMANI: If I ground myself in what I heard today and seeing both the sponsor and the FDA's briefing book, it seems like the inclusion criteria for A1c for the factorial study so where indeed to the combination of two drugs was used in those who didn't come into this on either insulin

or a GLP-1, it's something between a hemoglobin A1c of 7.5 to 10 or 7 to 9.

There are two studies that we can look at where this was tried. And it appears to have, from the data that we saw, reasonable efficacy and tolerability. So I do think the data that we saw here today gives us a starting point for whom this may be beneficial.

DR. SMITH: Dr. Neaton?

DR. NEATON: Actually, that was my same comment. Just to ask the clinical experts, if I'm listening to them correctly, so looking at this question, I looked at three trials here.

The first two pivotal trials and the trial where -- in the discussion, it came up, the person who has failed it already on a GLP agent. So what I'm hearing you say is that within those pivotal trials, there are a subset of people that would be candidates for a drug like this and that there also may be people who you first try the GLP inhibitor on that now the combination might work.

So those three trials are relevant to this

discussion. Am I hearing your comments correctly? Because I think there is trial data that's very relevant to what you're saying.

DR. SMITH: Dr. Budnitz?

DR. BUDNITZ: In thinking about this, I'm trying to put on my former first general internist hat and think about who would I start two drugs on. And I think along the same lines of situations where I could use a lower dose and try to minimize side effects.

But typically, that's with two drugs that I know are ineffective doses. I'm not quite sure yet that I've seen the evidence that low doses of the GLP-1 agonist is effective.

We've seen evidence that, in combination, it can be but that's just a whole that, when I put on my current medication safety hat, makes me wonder, am I exposing someone to, even if it's a low dose, unnecessary side effects or something that we're not certain is effective?

That's the way I would approach this kind of consideration.

DR. SMITH: Okay. On the other hand, just for some back-and-forth discussion here, if we think about how we approach patients who may be novel to therapy, who have type 2 diabetes, who have pretty inadequate control and we see them where we might even be considering starting them on insulin straightaway, very frequently, if those patients are -- particularly if we anticipate that those patients will have significant insulin resistance, which is most of them, very often we start them on metformin at the same time.

So we're not giving it in one injection because metformin is a pill. But we're actually simultaneously starting -- it's a very common circumstance of simultaneously starting two agents.

Metformin has side effects, and they are side effects that are problematic for many patients. So I don't have clarity on this myself, and I'm wanting this discuss this with some other endocrinologists. But I guess I'm raising the question of to what extent is -- now, metformin is a much more longer-standing drug that's been out

there a lot longer, but it has substantial side effects.

So the question is: How much is this hesitation, which I am feeling, how much of it is just because of the novelty of the two drugs we're combining rather than a data-supported concern about the side effects of, say, the non-insulin component of that?

DR. BUDNITZ: Can I just respond? So yes, it's not so much the side effects unknown. It's that metformin is FDA-approved and shown to be effective at the dose that it would start. And it's not clear to me that the GLP-1 agonist here is effective at the dose that we would start independently.

DR. SMITH: So I'll come back at you again on that. And when I start metformin, I would not infrequently start a dose that I do not expect to be effective, meaning that I don't expect it to be the dose where I'm going to end up.

But I'll start the low dose in part to walk into the potential side effects and have an

opportunity to observe them. And so again, one could argue that, if this combination is started with an intention of advancing it, that's one circumstance.

If it advances, then it resolves your concern about a possibly sub-therapeutic dose of one component. And if it doesn't advance, then a physician/patient combination would have the option of simplifying the regimen.

So in other words, if a very low dose seems to be satisfactory, then one could consider -- whether one would, I don't know that.

DR. BUDNITZ: So I think now we're moving into a second question, which is, well, why not start a single component therapy instead of being stuck with a fixed ratio? And then you can maximize effectiveness and minimize side effects, decide, if your patient matches the ratio that can be treated with the combination product, then of course, move to it. But you don't know that yet. So why not start with two separate agents? Then, if they converge in a ratio that's appropriate for

the combination product, then you run with it.

DR. SMITH: Right. I don't want to -- this is my last comment. I'm going to let other people talk.

But you can make the same argument about metformin and insulin. And very typically, we don't wait. So you could say, why don't I just start the insulin? Because the A1c is high enough, I think I'm going to need insulin in the game transiently or permanently.

But I also think I need more than insulin to optimize the response in this patient. Why couldn't you make the same argument for a GLP-1 RA component?

DR. BUDNITZ: Because the single agent, if that starting dose isn't approved --

DR. SMITH: Dr. Gelato, I think you were trying to make a comment.

DR. GELATO: No, I was just going to remark about the metformin. I mean, as a practicing endocrinologist, when I start metformin, I never start at 2 grams a day ever because nobody will

tolerate that. So you always start at a lower dose.

Quite honestly, if the patient is controlled at that dose and has done well on it, I don't see a need to go farther. But I sort of see this drug in a background where metformin is kind of there because I firmly believe that metformin should be in the drinking water, but I think it's a baseline drug.

Then you go on top of it with something like this that, for some patients, at a lower dose, could work well, and you've minimized both medications, hopefully maybe minimizing some of the side effects and still have an effect.

So I guess that's how I would look at it. But I understand your point because we don't know that for sure, although I do think there are data in the trials that indicate this drug is effective at lower doses than the maximum dose.

DR. SMITH: Dr. Wilson?

DR. WILSON: So I have a very, very similar thought process to Dr. Gelato. Endocrinologists

who see diabetic patients, we follow pretty much the script in that tableau I showed you that was up earlier. We don't have to put it back up again.

But there are lots of options and it's confusing to patients; it's confusing to general internal medicine physicians because this was expanded two or three years ago to include all these options.

The other concern, though, I have is for the person who is extremely heavy. I'm not sure where this new product fits in. So when we see a patient we can estimate how much insulin they might use or need to get effective glucose control even on top of metformin. If they're in excess of 100 kilos, we expect them to need more than 50 units of insulin down the line. When I picked that simple number, 100 kilos is 220 pounds.

I don't have a feeling for where this might fit in for somebody who's clearly in excess of that, 250, 300 pounds, because they have large insulin needs. And this combination product, we don't have an experience with large amounts of

insulin.

You may say that's not that realistic, but our colleague here, she did reach that weight -- and she's not that weight right this minute -- with another program. If you go into our diabetes clinics, we have lots of these patients. We have many patients over 250 pounds, for instance.

DR. SMITH: So other comments?

(No response.)

DR. SMITH: So I'll try to summarize, and then go on.

DR. GUETTIER: Can I give one more?

DR. SMITH: Yes.

DR. GUETTIER: I think one of the aspects to the question also asks you to consider why you would start this fixed-combination drug over the individual agents. I don't know if anyone else wants to provide comments on that.

So your choice for this particular patient is either starting one of the GLP-1 agonists which is available either as once-daily, once-weekly or a

basal insulin.

So why would you select this particular agent and how would you make that clinical determination when you're actually facing the patient in your practice?

DR. EVERETT: Just a quick response to that question and one that Dan raised earlier, because I'm not an endocrinologist, but I do something similar with antihypertensive medications all the time in my clinic.

I know it's relatively easy to ask patients to take two pills, and then once you figure out what the right combination is to combine them and give a fixed dose that's presumably better for adherence. But those are pills. Those aren't injections and so I think that might be one way to think about how the combination here is potentially advantageous to the patient.

DR. SMITH: Yes, Dr. Burman?

DR. BURMAN: I would say that in my practice as an endocrinologist, my personal view is I'd rather add on rather than start a single agent that

has both for the reasons mentioned. You might not need it, and you don't know how efficient they're going to be.

I certainly agree there are many circumstances where you're going to -- you think you're going to need or you actually need more than 50 units of insulin a day, whether it's obesity, or other lipodystrophy, or whatever circumstances we're talking about.

DR. SMITH: Yes, Dr. Wilson?

DR. WILSON: To build on what Jean-Marc Guettier just was asking, if someone, for instance, is on metformin and his A1c is in the 9 plus range, I'm probably going to need two agents, maybe more and maybe insulin is my real go-to if I can't get that person close to 7.

Now, as you saw through the tableau, I can start getting people to 3 and 4 oral agents. But I would think -- and I would be interested to hear what the other endocrinologists would think. The real strategy, a common strategy would be to go either -- if they're low 9's, I could easily reach

for a GLP-1 drug. It's that versus the others in that list for dual therapy.

Then let's say the patient got a partial response. I would have already been introducing the insulin discussions and I would say how about a combination perhaps, instead of just going -- this is where Brendan Everett was going.

He's on metformin. I've added a GLP-1, Victoza, let's say. And I said, well, I'm going to combine Victoza with the other. So I'm not going to go directly from metformin to a combo. I'm going to pass through the GLP-1 drug itself and then go to a possible combo.

But many of us would do exactly what Dr. Everett would; say, I would go metformin, I would go GLP-1, I might go insulin. And I'll say, now that I'm close to 7, Mr. Jones, we can combine that GLP-1 and the insulin probably with one injection and save you two injections. Instead of getting two injections regular, you'll get one a day.

That would be the more common strategy, at

least, I've found. I think I'm speaking for the way we would do this as an endocrinologist. We generally go one drug at a time, but then we will reassess and provide an option for a combination if that appears to be -- the drug is working independently in a patient.

DR. SMITH: So I think the problem there is you're discussing discussion question 2, which we're going to get to. And if we try to maintain this focus on what's specifically being asked, which is we have patients who are not on a GLP-1 agonist and not on insulin, now what I would say, trying to respond back to your question, Jean-Marc, is that it's something I would bring into consideration.

I share Dr. Burman's feeling. That's the way I also approach introducing drugs to patients, with caution and prefer to do an add-on. But where I would consider it myself would be a patient who I feel needs insulin, not a patient who I feel may be adequately controlled with a GLP-1 RA.

I think if I did it -- so I'm trying to not

say who I wouldn't give it. I'm trying to say who I would because I think that's what the question is asking. So there's a patient group and I just would -- and then I'd also commented earlier on special circumstances of where it may convince a patient to take -- whether I would do it, I don't know yet because it hasn't been an option.

So if you extrapolate to others -- now, where I'm struggling -- I'm supposed to summarize here.

But I'm not quite sure where to go because I don't think I have clarity from the panel members. I've heard comments, but I'd like to repeat a question for clarity. If we stay focused on this group that's not on a GLP-1 agonist and is not on insulin, beyond what I just said --

I heard comments about DPP-4 inhibitor failures. So is that what you would do? I'm looking at you, Dr. Wilson, but you weren't the only who said this.

So somebody who's failed a DDP-4 inhibitor, they're not doing well on a DDP-4 inhibitor,

they're not on a GLP-1 analogue, they're not on insulin, you would start both in them even though their A1c's in the 7 to 9 range?

I'm just trying to get clarity. I'm pushing for clarity here. That's what I'm doing.

DR. WILSON: To be clear, I would probably -- I do it all one at a time, especially for the person who might have already had a bump in the road, so to speak.

So after metformin, I tend to do things one at a time where possible. And if I'm very far from an A1c of 7 -- historically, most of us have gone to insulin for the short term, and then try to go back to something simpler.

DR. SMITH: So if I try to summarize with an open opportunity for people to amend my summary, that this has been a difficult question for the panel to answer, and it's been difficult to identify, with the level of experience that we have clinically, exactly which would be the target group.

Perhaps the most likely group would be

individuals who, in our judgment, require insulin. So perhaps there would be circumstances where we would introduce two agents. Although most of the panel members are resistant to that notion.

A circumstance that's been raised is from patient resistance based on concerns about insulin and weight gain, a patient prior experience starting insulin and then having said, no more, I'm gaining weight. But that might be a subgroup that, in fact, it would be reasonably comfortable to start both of these agents.

Given that one might argue that there is a parallel with co-starting insulin and metformin, it's possible that, particularly with increased experience, if this is ultimately approved, we would see adaption of co-starting these agents in the same way that metformin and insulin are started; although committee members also have expressed concern about that or discomfort with the notion that it is starting a drug, the GLP-1, at a lower dose than the accepted therapeutic range.

As a counter argument, we often advance drug

doses. So it's a complex issue with perhaps that small set of patients I summarized who might, with some confidence initially, be patients in whom this would be started, again, with neither of these drugs in the background. But with more experience, it may turn out to be a broader group. We just don't have enough data that support that.

Would anyone like to subtract or add anything to that summary of viewpoints?

(No response.)

DR. SMITH: Okay. I think we have time before the break to go on to discussion question 2. Again, I'll read it:

Discuss the benefits of using the combination product containing liraglutide and degludec 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 to an existing regimen.

In your answer, identify the patient population in whom use of the combination product in this manner would be useful. Explain your

rationale using data from the briefing materials and presentations or from your own clinical experience.

So now, we have a background of either insulin or the GLP-1 analogue and I know we've already discussed this to some extent but I'd appreciate some comments on where you stand on this question in the context of this question.

Dr. Burman, would you like to comment on this? Because I think we're getting --

DR. BURMAN: Sure. I'd be happy to. Thank you. I think the advantages of the combination are obvious with regard to cost, and single injection, and patient compliance.

I, personally, as I have indicated before, would prefer this approach of adding one agent on to another first to see whether the initial agent is effective over a period of 4 to 8 weeks or whatever and then add on the second agent.

That second agent could be adding on this combination or it could be adding on each element individually. So I think this potentially is a

role for this combination that we're discussing today. But which patient group is the hard one. And I think that's a difficult decision. I like what was said before.

I think, Dr. Smith, you had mentioned this as well, that patients who would prefer this approach, given that you always want patient interaction and discussion about what you're doing and the management, and especially if the A1c was minimally elevated in the 7 to 9 range, and you wanted to start this combination, individually, I think that would be fine.

For hemoglobin A1c's above 9 or 10, I don't think I would use this agent in a sequential way. I'd go to the standard therapy of long-acting insulin plus short-acting.

DR. SMITH: Yes, Dr. Meisel?

DR. MEISEL: Just a clarifying question, the fact that, almost by definition you'll having to lower the dose of the agent they're already on, perhaps by a substantial amount, does that factor into what you just said?

DR. BURMAN: Yes, it does. And I know that's a problem that we haven't talked about so much this afternoon. But it was talked about in the briefing booklet that, when you switch to this combination therapy, you may have to decrease the dose of the degludec component compared to what you were taking otherwise.

So I still would consider it, but would monitor the patient closely.

DR. SMITH: Yes. I would respond to that a little bit, too, because that presents a challenge and it's not ideal. But I do think we heard some about it from the open public hearing today, but certainly, from my practice experience as well, one injection versus two injections is a major issue.

I see Barbara Berney nodding her head as well. That's a big issue. And so, in a typical setting where one might be backing off on the GLP-1 analogue to accommodate a starting protocol, where insulin is coming in to the picture, in the context of type 2 diabetes, the risks of catastrophe, I consider to be very small.

So if one experiences a need to advance the dose, perhaps maybe if one experiences a little bump in glycemia as a consequence of that switch, I would anticipate that to be a modest impact.

So I wouldn't hesitate very much for that reason. So I think it's a reality and it's too bad it's there with the need to deliver in this way, but I think the upside of the single injection offsets the concerns and risks.

I understand as an alternative, one could consider giving basal insulin as a separate injection on, say, we're on the background of a full therapeutic dose of a GLP-1 analogue. And then after establishing an insulin dose, then one might be closer to therapeutic range for the GLP-1. That would be another way to approach the circumstance, to do the add-on with separate injections and then phase it in.

Maybe that would be safer and better, but I don't -- my guess as a physician, as an endocrinologist, would be that that wouldn't make a big difference probably. I'm probably splitting

hairs a little.

Other comments? Yes, Ms. Berney, did you want to comment?

MS. BERNEY: I just would like to say that I concur. Taking more than one shot is a major pain in the behind. But if you are a working person and you have to take a shot in the morning, and then you have to have a shot at lunch time, and a shot in the afternoon, by the time you are done with this whole experience, you don't want to take any shots because, first of all, if you don't have a place to store your insulin, it's a major issue and that was an issue for me. I had to bring a little cooler with me every day.

By the time I was done, I had so many punctures that I got infected. I have sensitive skin for another reason. It reinforced strongly enough that one shot -- and as many pills as you want me to take, I'll take -- more than one injection becomes a huge burden for a lot of us.

DR. SMITH: Yes, Dr. Reed?

DR. REED: Just in follow-up to your comment

about compliance, I think we all appreciate that. We can't forget about the issue of cost here.

I would ask the endocrinologists at the table, it would seem to me that, in reality, it would be a lot more -- it probably would be safer and more efficient in your ability to titrate the two drugs in an individual patient using the fixed-dose combo than either drug alone.

I pose that -- I mean, in the reality of how close are we really monitoring the patient.

DR. SMITH: I'm not sure. I'm not convinced that it would make in the end -- if we're dealing with a difference of adding an injection, ignoring the issue of two injections versus one but just adding a second injection, I'm not sure -- I wouldn't think there's a big difference in the challenges of managing the titration. The titration is going to be different obviously in what's happening.

DR. REED: I was actually thinking of the general practitioner who may not have the type of experience, and then how many different algorithms

there would be, and how many am I going to titrate the two drugs.

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

DR. PARKS: Actually, I have a question because I think that what we're struggling with this here are situations as what would be lost going from a patient who is not adequately controlled on either GLP-1 or a basal insulin and going directly to the fixed-dose combination.

To answer that question, sometimes we have to think about hypothetical situations. But I think in practice, they're not as hypothetical as we think. We're hearing that you see probably a lot more of these patients.

So bear with me for a second. If you have a patient who is on oral antidiabetic agents and is on, let's say, 40 units of basal insulin or degludec, that's a scenario, I think, that was in one of the patient populations studied in one of their trials.

If this patient is going to be switched to

IDegLira, then the initiation dose would be 16 units of IDegLira. That's a loss, a decrease of 24 units of basal insulin.

So would that be a concern and do we have data to really address that? So that's one hypothetical situation.

The other hypothetical situation is the converse. You have a patient who is on oral antidiabetic agents and maximum dose of liraglutide which is 1.8 milligrams, not adequately controlled.

So they're going to be switched to IDegLira. They'd be started on 10 units, so they're dropping from the maximum dose of liraglutide down to 0.36 milligrams of liraglutide. I think that get to Dr. Budnitz's question about loss of efficacy.

So I just want to make sure that the panel considers that in the background of the discussion.

DR. SMITH: Right. I think that's right on. I would ask if the -- so your first question gets at one of the challenges here, which is we're trying to define groups, patient groups.

Now we're talking about patients who might

be on insulin already. And so I suppose one of our challenges here is: Are there patients who are already on insulin for whom we would not consider this? And one key reason would be recognition of a capped dose of 50.

I would ask if the sponsor has any data from the trials in starting insulin doses and then the initial response that would help us with this.

DR. GOUGH: Yes, I can do that from Trial 3952, which, just to remind you, was patients coming in on insulin glargine between 20 and 50 units. Those that stayed on glargine stayed on a pre-trial dose and titrated up. But those that went to IDegLira went to the 16-dose. And you can see here, we've split the starting dose by patients on less than 30 units, 30 to 40 units, and greater than 40 units.

Even on these patients, at the highest dose of greater than 40 units, there's very little glycemic escape, if any, in the first two weeks. There's a little. It goes up a little bit in the first week, but by the second week and third week,

we're paralleling insulin glargine. I can also say that, in this trial, nobody satisfied our withdrawal criteria of hypoglycemia and had to withdraw from the study in the early weeks.

So we saw no glycemic escape in this early period. And I have similar data for patients transferring from a maximally tolerated dose of GLP-1 to the IDegLira combination.

DR. SMITH: So I think these data are helpful. And if I interpreted that correctly, we're up to 40 units of insulin at entry point.

Yes, Dr. Budnitz, please?

DR. BUDNITZ: Could you show that slide one more time? I just wanted to make sure I understand it correctly; is that okay?

DR. GOUGH: So the bottom curve --

DR. BUDNITZ: Do you mind if I ask a question?

DR. GOUGH: Yes, sorry.

DR. BUDNITZ: So for the top graph, on week 1, the folks that had pre-trial basal insulin going to 40 units, their fasting blood glucose went

from 140 to 165 or so; is that right?

DR. GOUGH: I don't have the exact the number, but yes. But then you see, by week 2, it's back to where it was in level with insulin glargine.

DR. BUDNITZ: Okay. Thanks.

DR. SMITH: So we do want to make a comment, Dr. Budnitz or anybody else, on having now seen these data and having read the question from Dr. Parks.

We've talked a bit, I think, already about patients on the GLP-1 to start which I addressed a little. But how about patients who are on insulin of the two agents? How would you define or can you define who would be the group that you would then advance to the combination?

I don't want to put you on the spot. If you don't want to take a stand, don't do it.

DR. BUDNITZ: I'm deferring to the endocrinologist on that.

DR. SMITH: Dr. Wilson?

DR. WILSON: So I think many of us would add

a single agent, could add the GLP-1 agonist on top. But patients often bargain with us and they say, "Oh, I'll do one shot a day but I don't do -- can't you come up with something that would be one shot a day?" And I think with very little downside.

So adding an insulin on top of a GLP-1, we sort of know what's going to happen. We don't anticipate any unusual side effects we're dealing with insulin.

Where I see that this, in fact, may have some uptake would be a patient seen at a general family medicine doctor or internist, not an endocrinologist because that's an addition that physician makes fairly comfortably and there's not a tremendous amount of titration.

The endocrinologist would also bring up the possibility of multiple injections of insulin and multiple glucose testing, which is more complicated. And if the patient had an infection, that really might be an issue.

But this is a step that a lot of internal medicine physicians could relatively comfortably

make. There's always a little more conservatism from endocrinologists, so we would probably add the drug and then potentially do a combo, as Ken Burman has said multiple times and also Brendan Everett.

But this could be a separate possibility, especially for the person who is needle-averse. And we have a fair number of patients like that.

DR. SMITH: So can you mark, just for me, what patients are you talking about?

DR. WILSON: Needle-averse patients, people who one injection versus two makes a big different.

DR. SMITH: They may already be on insulin, so yeah.

DR. WILSON: Yes, but then if you go to a -- if you go from one -- you still stay at one injection a day when you make this transition. That's the difference.

DR. SMITH: Okay.

DR. MEISEL: But is it reasonable to go from 45, 40 units down to 16 in that situation when you know that --

DR. WILSON: Yes. Dan Budnitz brought this

up. You're going to lose traction there for two or three weeks and then probably catch up. I would like to think there'll be some -- if approved, a product will develop. The experience for somebody already on an insulin, especially if you add this, is that you don't have to start it at a lower dose; you could start it at a higher dose.

But they have to show that that's safe and it'll be efficacious. It's a question of safety and to know how much you might change these doses. It's all very doable, but we don't have a lot of experience in their trial so far to judge other than what we've seen for adding this.

The only other caveat I would say is for somebody who's bumped up, and has an A1c 9.5 or 10, and is trying to fight an infection. I would be cautious just taking this route.

That may not be enough glucose lowering to help wound-healing and other issues where we really fight to have tighter glucose control. But for many patients, this may be a possibility, yes.

DR. SMITH: I have a quick question for the

sponsor. You showed us fasting glucose data. Can you tell us anything -- I don't want to take much time for this -- about post-prandial glucose data during this transition period?

I realize we think about fasting glucose a lot with basal insulin but, if we're trying to understand the impact of backing off from 40 units of insulin, it's important to know what the peak glucose levels are also.

So do you have any data there that might help us?

DR. GOUGH: I don't have data in that initial period, but we do know obviously that this does affect post-prandial glucose and has a significant effect on post-prandial glucose excursions.

I showed in the core presentation this was the standardized meal where you can see the lowering of the post-prandial glucose. And I can support this with continuous glucose monitoring data as well over three meals.

DR. SMITH: But I was specifically wanting

to know about the impact of the step-down as one does the transition --

DR. GOUGH: I don't have that for --

DR. SMITH: -- and to really understand that.

DR. GOUGH: -- the first few weeks, sorry.

DR. SMITH: Ms. Hallare, did you have a comment in this discussion point?

MS. HALLARE: I have a comment with regards to us talking about weight. But I also notice, for instance, on slide 94 from the sponsor that IDegLira has a potential to lower systolic blood pressure.

Also, I heard while this was being discussed by the sponsor that cholesterol and/or triglycerides could be lowered as well. So that could be a factor in, I mean, as in clinical benefit of the weight loss, not just BMI, but also the other correlation, like for instance whether it's related to hypertensive effects or other health-related aspects.

DR. SMITH: Dr. Burman?

DR. BURMAN: I just wanted to comment that I appreciate the slide that was just shown. But I have concerns. As you just mentioned, it only shows fasting blood sugar. You don't know what the excursions are throughout the day and how glucose homeostasis is for 24 hours when you decrease from 45 units to 16 units. And these are clinical trials, not real-life experience, so it's hard to extrapolate.

DR. SMITH: So I would propose I try to summarize. And I guess I would start by saying that probably the panelists share with me the feeling that it would be nice to give a more directive clear summary and advice to the FDA than we're giving on this one, but I don't think we can.

There is generally more acceptance of the notion that there may be significant patient populations among individuals who are on either insulin, and not a GLP-1 agonist or a GLP-1 agonist, and not insulin in whom a transition to this combination might be acceptable.

There's uncertainties to all of these

considerations because of some limitations in the data. But it would perhaps be most comfortable in the case of patients who are on a GLP-1 agonist who then may transition to the combination recognizing that it would mean initially a lowering of their dose of the GLP-1.

For patients who are on insulin, it's not considered. There may be a significant population in which this would apply. But the group found this difficult to navigate in terms of defining that patient group, although data presented showing that patients on as much as 40 units of insulin at the time that they undergo a step down and a transition to the combination by fasting glucose appeared not to have severe adverse effects of that transition.

Those data are still somewhat incomplete in terms of understanding fully the impact on their blood glucose profile.

We didn't discuss this in detail, but with the data available, it's difficult to define a level of insulin, a dosage of insulin that is where

we would start it and a dose where we would not.

Clearly, one of the concerns is which patients would ultimately end up requiring more than 50 units of insulin, but it's more complex than that and perhaps not fully understanding how this transition is navigated in terms of its effects on glucose control.

Then other factors inevitably have to be taken into consideration. So Dr. Wilson mentioned that patients who have an acute problem as such of an infection that may be an explanation for their elevated glucose levels. A complex program like this might not be how we would respond.

Additionally, factors that would influence it would be the patient themselves and their potential aversion to two injections versus one, as well as the appreciation of that as an issue by the physician.

So those are all operatives. As Ms. Hallare mentioned, we need to consider the sort of full profile of effects which our ability to process is a little limited at this point. So likely, this

would be on a larger group than discussion question 1. And it may be a very substantial group, but it's difficult for us to really define that.

Is that good enough? Are we doing well enough for the FDA on this one?

DR. MEISEL: I know it's not being proposed, and it's probably not technically possible, but if this were designed in a way where the one could be fixed and the other one could be variable, would that change any of the conversation here?

DR. SMITH: Well, the problem with that is that that is not something that one can do with a snap of a finger. It's a long journey. I mean, that's not something we can consider today.

I'm going to wrap this up pretty quickly. We have a comment from the FDA.

DR. YANOFF: You brought up some interesting points, which made me think of something that was not part of the question. You asked about patient populations for whom this product may be useful, but raised the issue of prescribers, different types of prescribers. And I think Dr. Everett

raised the point that a less complicated regime could be important for some prescribers.

I don't remember if there are any further comments on, as a non-endocrinologist, if you think this would be easier to use and may be more likely to bring up to patients who would not have otherwise received it, these two drugs.

DR. SMITH: Yes, Dr. Yanovski?

DR. YANOVSKI: Yes. I don't know the numbers. I would imagine that most patients with type 2 diabetes are not treated by endocrinologists, but are treated by their primary care physicians; is that correct?

DR. SMITH: That's correct.

DR. YANOVSKI: Yes. So I think that that actually is an issue in terms of simplicity and might lead to more primary care provider acceptance of an injectable for their medication if they don't have to do quite the degree of titration.

DR. SMITH: I think it's a consideration. I don't know how different it really is for a non-specialist group. It's worth thinking about

that but it's hard for that to have clarity for me because in some ways, it's easier to give one injection of one agent.

In another way, it's more complicated to process and respond appropriately to the potential consequences of changing the dose of one while advancing another. So I don't know if that's not, from my perspective, kind of a wash. There may be preferences for people. They might go to the easier, simpler route. A single-injection route might be very appealing to them, but I just don't know that.

So I'd like to wrap up if I can. Just a quick comment because I want to keep this in schedule.

MS. BERNEY: Well, I don't go to an endocrinologist. I do see an internist. And one of the gentlemen who presented from the public said that there are some internists, some doctors, they are insulin-phobic.

It took a long time before my doctor ever even would consider it because of all the other

things I was taking. I think if I were a patient who came in had an 8.5 A1c or something higher and he knew that metformin wasn't going to do it, I think knowing him --

I'd been going to him for many years. I think he is just exactly the kind of person who would say, Oh, this looks like something that we could do. And he wouldn't be as phobic about the insulin because, every day, I was increasing my dose.

He was not comfortable with this at all, and he treats a lot of diabetics. I guess I must not be a normal run-in-the-mill patient. But as an internist -- I'm not an endocrinologist -- I think he'd be far more comfortable with something that was a one-shot deal.

DR. SMITH: Okay. So I am going to close the discussion on this unless there's urgent -- or a request from the FDA.

We're going to take a break. This will be a 15-minute break. It's 3:40. We'll be back here at 3:55. Let's make it a 10-minute break if we could

so that I'm sure we have enough time for the final two questions. So let's come back here just a little bit past 3:50.

(Whereupon, at 3:41 p.m., a recess was taken.)

DR. SMITH: So we're back in session. Dr. Budnitz wanted to make a follow-up comment.

DR. BUDNITZ: The only thing I was going to add is just it is very hard to think about what internists will do as one group. There's slower adopters; there's quick, fast adopters of new therapy. Speaking as, I think, the only internist here, I don't know what we would do as a group.

DR. SMITH: So we go to discussion question 3. 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 degludec, with a drug that, when used alone, has one or two recommended effective doses, i.e., liraglutide.

Specifically discuss, in the first box:

Issues related to a 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 50 units.

Then in the second bullet there is issues related specifically to product presentation. Let me stop there and let's come back to that one separately. Let's do the first part. And as Dr. Guettier mentioned this morning, comment any broader concerns here; also about safety issues should be expressed here.

So what I would suggest for reasons of efficiency, so we have enough time to discuss the second part of this and the voting question, that I think we've already discussed a substantial portion of this already.

I think we've addressed concerns about the insulin dose being limited to 50 units in many of these transition questions, so I don't think we

should retread that ground and people should add any further comments they wish.

I would start out with, one, which is that in terms of consideration of broader concerns and based on the data that we have reviewed, I have not seen evidence of safety issues that would not be anticipated from the individual drugs when they're together in this combination, either new safety issues that would not be in the picture until now we have the combination drugs or the magnitude of issues of safety concern.

At least from me, from a general safety perspective, where I feel like I'm a pretty cautious person, I have not seen things that give me concern about the drugs in combination beyond the fact that initiating two versus one brings both together.

But I'm not concerned from the data we have. And more would come from experience with the drugs if the combinations approved. I'm not concerned about a new set of safety issues.

So any other comments that would summarize

and would be pertinent to the first part of this, not the device which we're going to get to.

Yes, Dr. Cooke?

DR. COOKE: I'd actually like to address this question about whether the lower doses of liraglutide have any glucose-lowering effect because it seems like the conversation around the table is that there continues to be a lot of confidence that it doesn't.

But the data from the pivotal trials for the combination in that factorial design, especially with the addition of the phase 2 data from the liraglutide, really give me some comfort that these lower doses actually do have some glucose-lowering effect.

Now, they might be sufficient in it of themselves to justify FDA approval as an independent agent, but I'm actually fairly -- I don't know if "convinced" is the right word since the factorial design trial investigation of that question is certainly problematic.

But I think there is reasonable data to say

that the lower doses do have an impact and contribute to the effect of the combination.

DR. GELATO: I absolutely agree with you. I think it does, and I think that this could be an effective combination for the right group of patients.

I think we're all struggling with: Who is that right group? But I do think that there is efficacy at the lower doses so I don't think you would be giving somebody a drug that wouldn't be effective at all and just saying, well, wait until we get to 50 and we'll see an effect.

I agree. I think there is efficacy at the lower doses.

DR. SMITH: I would say that I agree with that. I think we just don't know. I think it's quite likely and compelled by the data that we've seen. But I don't think we've had an answer, from my perspective, to that question. But I think it's quite likely.

Was that on exact same point? Okay.

DR. STANLEY: I was just going to say that

the side effects are also dose-dependent, you know, the ones that we worry about with nausea and GI side effects. So the lower dose, it has a little bit of effect on lowering A1c, but also has a rather minimal effect on GI side effects.

DR. SMITH: Dr. Reed?

DR. REED: Well, when Dr. Cooke was talking, I was going to agree. But everything that has just been said was what I was going to comment on.

What I don't understand in our discussion today is that we continue to talk about this as a single drug product. We may want to talk about the insulin drug or we may want to talk about the GLP drug.

To me, it's a combination product. And although there is insufficient data, in my opinion, as was opined by the sponsor to take a position on additive or synergy, I doubt from what we saw of the data there's synergy, but there is compelling data to suggest an additive effect here and that they are working in some way in harmony at these lower doses.

I mean, I applaud the FDA in their critical assessment of this data. But as simple as just following the trends gives you, I think, what Dr. Cooke was getting to, that it's somewhat compelling of this drug combination.

I think we need to think about it as a combo than either drug alone. And it's the fundamental principles of an additive or synergistic effect of how do I get that with at lower concentrations if I can.

I think it's very important, what was just brought up, that there's no question of the dose-dependent intolerability, and poor clinically relevant side effects of the GLP agent, and that this combination is able to get you that effect.

What has been most compelling to me, frankly, was the excursion data where Dr. Gelato brought up about the discordance between the self-monitoring plasma glucose, which we know all those variables, relative to the A1c.

Maybe it is that. And I'm speaking as a non-diabetologist, but maybe as that excursion

data, getting that greater control over a longer period of time and then translating to your primary endpoint of A1c. But it's a combo.

DR. SMITH: Dr. Neaton?

DR. NEATON: I just was going to comment on the combo and the toxicities. Actually, I was pretty impressed with slides 82 and 83 where in 697, the level of toxicities with the combo in terms of the typical side effects that you see with the GLP antagonist are substantially decreased.

So the combo, there are fewer withdrawals, for example, to GI AEs and, it appears, substantially less nausea early on.

DR. SMITH: But do you feel confident about whether that was related to an effect of insulin in the combination, or the combination, or just simply the dose of the GLP-1, which is associated with those symptoms?

DR. NEATON: Well, it could be just the dose. I mean I guess I'm agreeing with Dr. Reed. Let's look at the combination. The combination here seems to have some efficacy, it's clear.

But it also has some advantages with regard to toxicity on both sides of it, the hypoglycemia, the weight loss and the GI toxicities.

DR. SMITH: Other comments?

(No response.)

DR. SMITH: So in regard to the first part of this question and the first bullet, not restating the points that we've made in the earlier ones, there seems to be in general not substantial concerns about the side effects, the safety issues based on the data that have been presented.

There is not unanticipated safety issues. It's acknowledged that, as part of the dosing regimen which advances from a lower level, the dose of this, that reduces the side-effect risks. They seem to be dose-related. So that's a positive that again makes this all feasible.

So anything else to that? I think I would move to the second bullet, which is really a slightly different topic:

Issues related specifically discussed, issues related specifically to product

presentation/device, 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.

So this is open for some comment.

Dr. Budnitz?

DR. BUDNITZ: So these are some medication error comments that I think could be addressed. Two comments, one is I think there's a cap on the maximum that can be dispensed.

Was there consideration of putting a floor at the lowest dose that could be dispensed at 10 units if that's what the recommended lowest dose is? So that's maybe a question or something for consideration.

Then the second point is this unitless number. I think that is problematic because I guess we don't have those pens in front of us anymore but it does give us -- on the pen, it lists

two active ingredients and then a unitless number. So there's opportunity for confusion about what that means. I understand there's just the logistic or the practical matter of, you can't put too many number on little tiny window.

But one potential suggestion is, if we're calling this thing, I don't know, a dose step or whatever units are used in the instructions for prescribing, to put that just in a sticker or something around it just so you can see those numbers refer to something, whatever is described in the package insert or directions.

But I do have concerns about a unitless number that can easily be confused with two labeled ingredients that are right there. Does that, whatever you dial up, refer to that insulin component or the other?

DR. SMITH: Dr. Meisel, this is kind of coming in your zone here.

DR. MEISEL: Well, even a practical matter, so you're going to enter an order into a computer. I want to give 16. Well, 16 what? Every computer

will require a unit of measure, right?

I'm not sure if the computer companies are going to be happy about coming up with a new one called "dose steps" or something. We need to come up with something that's different.

I could also see that the fact that this is a combination of two different drugs being real apparent to an endocrinologist, but really lost on an orthopedic surgeon who's admitting somebody for a broken leg at 9:00 on a Friday night and wanting to continue home medications. And then there's calls of blood sugars high and they're doing all sorts of things that they shouldn't be doing.

So I think we need to get into the real world of practicality of how a product like this will end up getting used in a large population and make it real clear that this is not just insulin, but this is two medicines with unique profiles.

You don't go and add Victoza to this. And then if patient reaches 50, you can easily see a person who doesn't know what they're doing saying, well, add 10 more, and so then they're getting two

shots. And whether they go and add Lantus to this and that, you know, all sorts of things will end up causing all sorts of -- I can see the med-error reports flying in to my desk today --

(Laughter.)

DR. MEISEL: -- if we're not real careful about the dosing units, the maximum dose, what's really in this thing and make that real clear.

I think the use of the pen, I think that was talked about before, the human factor. That's easy. This is a standard pen that's going to be easy to dial and give. But it's the understanding that this is not just insulin. This is something else.

DR. SMITH: Dr. Burman?

DR. BURMAN: My concerns were somewhat assuaged by the human factors report, which was really pretty good. But I also wonder whether it's possible to suggest a REMS program for healthcare providers who are prescribing the medication such as there is, I know, with vandetanib, to name one. I think that's very helpful and I know it's

somewhat laborious, but it actually only takes five or 10 minutes and it teaches you what you need to know.

I think this is so complex for all the reasons brought up. I wonder whether a physician or a healthcare provider should just be able to prescribe it without some other knowledge.

DR. SMITH: Would the FDA want to comment on venturing into that territory?

DR. GUETTIER: Sure. I think the issue of REMS -- REMS, for people who don't know what REMS are, REMS stands for risk evaluation mitigation strategies. They're authority that we have to mitigate a problem that we foresee with a product. And usually, they're reserved for serious products after you've maximized labeling.

So the first thing we would say is to maximize labeling and that's the first thing we would do for a product. And then we would ask what is the purpose of the REMS and what is the REMS intending to achieve because that would likely determine what REMS we would actually recommend.

With REMS, there's a panoply of options that we have, and one of the potential REMS element that we have is something called an element to assure safe use, which would actually restrict the distribution, et cetera, et cetera, the prescription; we could enforce a physician to get trained.

If we're going to go to that extent for this product, then we would probably need to know that this product is addressing a very important unmet need because that is both a burden on the healthcare system and it would be a burden for prescribers to prescribe this product.

So this certainly is an option that we have to consider. And if you're going to go that route, we'd like you to provide maybe a little bit more detail and granularity on exactly what you mean with regards to what you would like to see with regards to training to address maybe some of these errors.

DR. SMITH: Thank you. Other comments?

DR. MEISEL: Just a point of clarity about

that, the prescribers in this case will be very broad because we've got to be thinking beyond the endocrinologist and even the internist who's prescribing it de novo.

It's the people who are continuing it, the hospitalists, the orthopedic surgeons, the whoevers, the nursing-home doctors, whoever they may be that would be continuing therapy, started by somebody else. But they're still put in the business of prescribing it, and monitoring, and doing all the other kind of work.

DR. SMITH: Dr. Yanovski?

DR. YANOVSKI: In terms of labeling, many of the patients are going to be obese, and some of them maybe on Saxenda, which is the higher-dose liraglutide for obesity.

But both they, the patients and their doctors, may be thinking about as an obesity medication and not a diabetes medication. So I think it's going to be really important to have that really largely labeled as a contraindication of combining the two.

DR. SMITH: Other comments on this point? Yes, Dr. Reed?

DR. REED: I was just going to say that I concur on the issue of no units or no -- I think there has to be a unit. I may be a little more cavalier. I'm not so concerned that it has a partner agent that I don't know the unit to.

Unfortunately, I'm old enough that when trimethoprim sulfa came out, it was all dosed on the sulfa. The pediatricians had no clue what trimethoprim was until we figured out that was more important than the sulfa component. And then we dosed it on the trimethoprim component.

So I'm a little more cavalier on that, but I think it is important for unit. But I also think here I really don't have a concern of maximum dose for the combination as capped because it's not the combination. What's the capped is the product.

Before, you're bringing up issues about, well, I may need more than 50; I may need more of this drug or that drug. But once it's capped on this unique product, it's out to using individual

products and titrating it further.

So I don't see that as an issue. It's just this product is capped. The sponsor may decide that later on they want to release a different product, more flexibility in the product.

DR. SMITH: I would just respond to that by saying that I think one of the important issues with the cap is the potential that that would influence decision-making on who to start on this.

I understand it's pretty straightforward. If someone is on this combination, and they reach the max, and they're not adequately controlled, and it looks like insulin is what would be a better drug to -- the component to increase, then one would very logically get there. But knowing about the cap in advance, I think that's why we've been discussing that issue. That can influence some of the frontend decision-making on who to start and who not.

DR. REED: Yes, I can see that. And actually, on the other end as well, it might send a signal that this is it, that cap in general across

the population. I can see that, too.

DR. SMITH: So I'm going to try to summarize, and we can add to my summary. But my reading of this is that perhaps the primary concern -- there's concern about potential confusion by users, including patients but importantly including physicians.

Those might be the primary prescribing physician, but they may also be a physician who enters the care of that patient and did not initially prescribe that drug, the example having been a surgeon caring for a patient who's been admitted to the hospital for some acute issue.

I think there is sort of a leading core of concern, which is the importance of having the key users understand that there are two different drugs contained within this combination and a recognition and non-confusion about that, for example, not thinking of this just as insulin.

As we sort of discussed and expanded on that problem, there was a lot of discussion about, without solving and answering all these questions,

issues of labeling.

As a component of that, it's how to label a dose, but it's a really bigger issue which is how to label and describe the product in a way that people get it and understand what's there, whether it has to do with a dose that they're giving, or a dose adjustment they're making, or whether they're confronted with a patient on this and need to decide what do I do now with this hospitalized patient.

So labeling becomes a primary kind of question and strategy in terms of trying to resolve this issue of understanding that it has two different drugs in it and that they need to be appropriately managed.

The question was raised of considering a REMS and I refer that to the FDA because this really does bring another level of expense, complexity, complication and is something one should consider if it's necessary.

But unless it's obvious that that kind of thing is necessary, I think one would first

vigorously pursue the questions of how labeling can resolve the concerns that we've been hearing about.

Appended to labeling are the issues of strategies for educating users. That's, in a sense, part of what I'm viewing as labeling.

So I'll stop there. You want to add to that?

Yes, Dr. Budnitz?

DR. BUDNITZ: Maybe this is for the sponsor to address. I'm just curious what the rationale was to putting a cap but not a floor. If the recommended dose is between 10 and 50 units or whatever, why have the option of dialing up 1, 2, 3, 4, 5, 6 units?

DR. GOUGH: The cap of 50 is obviously so that patients can't go above a dose of 50. With respect to the lower cap, I don't think we needed one. In fact, some patients did titrate below 10.

We did have some patients, not many, but we had a few patients on a dose of less than 10 of IDegLira. So it can be used at those doses.

DR. BUDNITZ: So for what might be off-label

use, just to clarify?

DR. GOUGH: With respect to the label -- and this is for a discussion on another day -- we investigate -- we had a starting dose of 10 and a maximum dose of 50. But in the clinical trial, patients did titrate below 10.

DR. BUDNITZ: Right. So I guess the point is, whatever the lower dose might be for what has ended up being the recommended dose in the label, I just wanted to make sure I understood the rationale for having a patient being able to titrate, to select a dose that's not one of the indicated doses.

DR. SMITH: Okay. So we're going to move on to the final question, which is a voting question. And we're going to use an electronic voting system. Once we begin the vote, the buttons on your microphone will begin to flash and they'll continue to flash even after you've entered your vote.

So what you should do is press the button firmly that corresponds to your vote. If you're unsure of your vote or you want to change it, you

can press the corresponding button, the new one, until the vote is closed.

After everyone had completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Then we're going to go around the room and each individual who voted will state their name and their vote into the record. And at that point, you can also state the reason why you voted as you did if you wish to do so. We'll continue in that manner until we've made our way all the way around the room. So I'm going to read the voting question:

Based on the data in the briefing materials and presentations at today's meeting, do you recommend approval of the liraglutide/degludec fixed-combination drug delivered using the proposed device 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 who have never been treatment

with a basal insulin product or a GLP-1 product, for patients who are inadequately controlled on either a basal insulin product, or a GLP-1 product, 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 start voting, are there any questions about the clarity of the question itself?

(No response.)

DR. SMITH: All right. So we can go ahead with the vote.

UNIDENTIFIED SPEAKER: Can we have everybody press the button one more time?

DR. SMITH: You want everyone to push it one more time? All right. Everybody, push the button one more time.

(Vote taken.)

DR. BONNER: For the record, 16 yes, zero no, zero abstain.

DR. SMITH: What we'll do is we'll go around the room and each person, what you should do is activate your microphone, state your name, state your vote. And you can make any comments you wish about your rationale for the vote.

I think we'll start with Dr. Nason. Sorry. Everybody complains when I start with them.

DR. NASON: It's all right. I just think the clinicians in the room are going to have such a better way to speak to some of these issues.

I'm not a clinician. I definitely defer to my clinical colleagues as to many of the complications that come up with exactly who would be started on this or who would be a candidate for it and how it would be managed.

But it seems clear that there is a place for this in some group of people. It seems more obvious on people who have sort of stepped into it by starting on either insulin or GLP and have a reason to go on or want to possibly dial back the insulin they're on maybe with a little increase in the GLP or the dial back the GLP, I guess, with a

little increase in the insulin.

Those people, it seems more obvious rather than the question of anyone who's coming into it new as their first injectable. But again, I will defer to my clinical colleagues.

I thought the data were pretty data convincing with a few tweaks that maybe I wish had been a little bit clearer. But it seemed pretty convincing that there's a place for this and that it does seem to work as one might expect from the combination.

I'm Martha Nason, and I voted yes. I guess I forgot to say that at the beginning.

DR. REED: This is Michael Reed. I voted yes. I too will yield to my diabetologist colleagues for much of this. I want to thank the FDA for a very critical review of the data.

I think it was thoughtful; it was critical. You brought up a number of issues relative to the data. I also would like to compliment the sponsor on the data they brought to the table. But I think all of us as clinicians and scientists, no matter

how much data you bring us, we want more. What I found compelling in this data, as we've already talked about, has been the trends.

Obviously, on a pharmacologic basis, the combination is very rational. It makes sense. I think the data is compelling, both at dose and in safety. Where it's going to fit in the therapeutic armamentarium, as I said, I will yield to my diabetologist colleagues.

But I think as Dr. Wilson brought out and reminded us of the stepwise paradigm or the treatment of adult type 2 diabetes paradigm, you can go look in those columns and see very clearly, I think, where this drug would fit today.

To me, the question is where it may, in fact, fit tomorrow, looking at this combination and the dose opportunities with it.

MS. BERNEY: This is Barbara Berney. I don't think my vote counts, but as a patient, as a patient representative, I have to defer to the professionals in this area. But as a patient representative, I believe that it would be just

another really wonderful addition to the arsenal. And I think it would aid in patient compliance and simplification of people's lives, as well as the savings to their pocketbook.

DR. YANOVSKI: Susan Yanovski from NIH. I also voted yes. I think the combination met all the criteria for efficacy. I think that it had fewer side effects than the individual components due to the lower doses and also had the advantage of having a once-daily dose that might aid in compliance.

As far as the patient population, I kind of have mixed feelings about its use in people who are only on oral medications and going right to the two doses.

But I do agree with Dr. Smith that there could be individual patients in whom that would be appropriate. I see it primarily being useful in patients who are already on a GLP-1 agonist or insulin and require intensification.

DR. STANLEY: This is Charlie Stanley. I voted yes. I mean obviously, as a pediatric

diabetologist, I don't have a lot of experience with these agents for type 2 diabetes.

But what I'm impressed with this product is that we're not -- in our usual talk about in improving hemoglobin A1c by 1 percent, we're actually talking about possibility of normalizing fasting glucose and hemoglobin A1c.

I think that's maybe a new era for type 2 diabetes. I think it's pretty clear from the data that, as an add-on to the either basal insulin or GLP-1, it would be useful. And I think it will probably be a very useful add-on to single-drug metformin without going through first steps with either insulin or GLP-1. But I think that that may take some experience if you have a diabetologist getting used to that idea.

DR. WILSON: Peter Wilson. I voted yes. Just a couple of points, mostly, maybe some gaps and unanswered questions. One is in titration studies, we're used to looking at 26-week data.

But with titration for glucose and A1c as the metric, perhaps we need data a little longer

than that for the collection so that the 6-month data are really solid in terms of what it means for the patients. That's number one.

Number two is, I would love to see a 12-month plus weight data for this combination product because we really may be entering an era where that could have tremendous application with an insulin that perhaps even beyond 12 months, that the patients don't gain weight the way people do on other insulin types of regimens.

I do have some concern about people who are very heavy and whether they will be able to use this because they will need -- and this is where an endocrinologist would assess that they are going to need greater than 50 units of insulin -- total insulin rather rapidly.

Starting with a lower titration, they're going to go zip right through 50 and then the patient would be dropped. That needs to be sorted out fairly quickly, maybe a post-marketing project.

So I think you could get the answer fairly quickly on that because it could lead to

discouraged patients and discouraged physicians. You get a very heavy, very insulin-resistant patient, you try to use the drug, and then you're just not able to get very far with it.

I certainly think it will help with what we call in endocrinology insulin inertia, the uptake of using insulin. This is a big issue. It tends to be only endocrinologists who initiate insulin.

This ought to widen the scope for that. So that's plenty. Thanks very much.

DR. MEISEL: Steve Meisel. I did also vote yes. I see the value of this more for the patient who we can add a third drug to and it's easier to do it in one shot as opposed to going from metformin for a dual therapy.

So if I were to parse that question there, I'd be more inclined to approve it for that as opposed to adding two drugs right to metformin. I think that's a problem.

I think as Dr. Wilson said, we need some better guidelines and I'd rather see them before the drug would be marketed. So if we can find a

way of doing that with some additional data about patients who it just aren't appropriate for, the patient who is going to need 75 units of insulin or 80 units of insulin, that sort of thing, whether it's based on their weight or their prior insulin dose, or whatever it may be, I think we need some better guidelines on that piece.

No surprise we also need some error proofing in terms of the dosing and the dose units, and clarity about that these are two drugs and not one drug, and people aren't referring to this as plain old insulin.

One item that I have a minor concern about that we didn't talk about today, sort of buried in the sponsor's briefing book, was the fact that there seemed to be more skin cancers in patients who are on this product than anybody else.

There's a comment that's there's no plausible mechanism for that and that's probably true. There is no plausible mechanism for that, but it doesn't mean that there isn't an implausible mechanism for that that's still related.

So I would encourage the FDA to be looking closely at that post-marketing to make sure that there isn't something there that we don't become surprised about.

MS. HALLARE: Diane Hallare, consumer representative. I voted yes, and I voted yes because of the stabilization rate, the seemingly low side effects at this time, the efficacy results, the weight loss, and systolic blood pressure decrease, the few events of severe hypoglycemia, and the improvement of patient's quality of life including with regards to body weight, the number of shots they have to take, and also less stigma, which can result in better medical adherence to the combination which would result to proper management of diabetes.

DR. GELATO: Marie Gelato. I also voted yes. I think that the data did show that this drug met its efficacy endpoints. I was impressed with the fact that people who are on insulin were able to get their A1c's to target with this drug, even though it was something I wouldn't have thought.

I would have thought they would have needed more. I think the combination, as been said, has some either additive or synergistic effect that we might not understand.

I also think that this could be a drug that be used for people who have failed orals, or people who have failed insulin, or people who have failed the GLP-1. I think it's going to take the clinician, the patient, and also the use of the drug to try to define that as we go forward.

But I do think diabetes is a tough disease and I think we need all of the things we can muster to get it under control and keep patients from developing complications.

DR. SMITH: I'm Robert Smith. I voted yes. I feel that this does bring a new useful treatment option and in that way meets an important need. I was not concerned about safety issues as I stated previously so that didn't cause me hesitation in voting yes.

Sort of several issues in discussion of the labeling, I would encourage some consideration in

the labeling not knowing what you've already considered about providing some kind of guidance for patients who are already on insulin, some guidance in regard to dosing, whether there's a dose level at which it should not be used or a dose level it should be used with caution, some sort of perhaps caution, but some sort of guidance.

There was a discussion from the FDA of labeling comprehension studies which probably can be done fairly quickly. And that may be a useful part of working through the labeling issue, to not just talk about it, but actually get some data along the way.

In terms of post-marketing studies, I don't think I could sit here and devise a good post-marketing study. But the thing that I would consider is trying to adequately structure some kind of post-marketing study, at the minimum some data collection, but preferably some kind of a study which would look at patients who are not effectively treated by the regimen.

I've left that purposely kind of broad, but

it's really trying to probe, presumably if this is approved, as this is used, they will be patients for whom it's discontinued, it doesn't work. And it would be of some value to try understand who those patients are, whether they're the markedly obese subjects, or whether they have certain entry insulin levels in their regimen, or some other characteristics.

So that's pretty far from being specific, but I would give some careful thought to whether that can be molded into a useful post-marketing study or two, or whether it could be adequately addressed by some form of monitoring, which I don't think it can.

DR. EVERETT: My name is Brendan Everett. I voted yes. I think the sponsor did a reasonable job of demonstrating efficacy. We know that these therapies are effective by themselves.

I think the combination also seems to effective at lower doses and with lower side effects. So I think those data are compelling.

I have serious concerns about the extent of

missing data. And I anticipate and I hope that there is not a similar extent of missing data in the LEADER trial, which may or may not be presented in this forum in the future.

I also show the concerns that the FDA raised about imbalances in dose stabilization in terms of the rate of titration -- the rate of running of the race was the analogy that was used -- and some effects that those have in terms of biasing the results at the end of the study.

I think those are very real concerns, but they didn't, for me, trump the overall evidence of efficacy.

I tend to agree with many of the people who have gone before that the populations or patients that this should be used in is those who are either one of these two injectable medicines already, in particular I think the GLP-1 agonist.

I think there's probably some room for using the combination in people who are already taking insulin, although I worry that you're effectively removing an infinitely titratable medication for

one that has a much smaller therapeutic range.

You're going to use that for a period of time before it, again, runs out of efficacy just because you're limited in terms of the maximum dose.

That brings me to my last point, which is not dissimilar from what Dr. Smith just said, which is that I think, in that population who is -- I hate to use the word "fails" -- not adequately treated by this particular regimen, in other words requires a dose of 50 units or higher, some kind of post-marketing study. What do you do with those patients?

Do you transition them back just onto insulin? Is there a particular subset of patients that is identifiable prospectively so that you know that the combination therapies may be not the best agent to choose in that group?

Again, I'm leaving that relatively broad, so thank you.

DR. LESAR: Timothy Lesar. I also voted yes. On balance, I thought the patient

satisfaction, safety, efficacy, and potentially reduced cost certainly outweighed some concerns about data on adverse events, about potentially using unneeded combination therapy. But on the whole, I believe the benefits outweigh those risks.

I think there are some risks in terms of how this drug is used, so it's quite important, I think, that caregivers and patients understand the nuances of starting this medication, giving them the different scenarios that were discussed.

Also, I think I had some concerns related to the naming of those drugs and the dose expression as I stated. The name might be important, particularly in the age of e-prescribing, in which we face character restrictions and long pick lists that oftentimes wrong selection of the drug may occur from, when it is being prescribed in that manner. Thank you.

DR. NEATON: Jim Neaton. I voted yes. I thought the five trials kind of established the benefit exceeded the risk. I share the concern about the missing data and I think it's kind of

unacceptable these days not to collect data after people withdraw from studies, particularly a 26-week trial.

I thought the FDA had some very good points like the external validity, and so that was the toughest part for me. I think, as I mentioned this morning, the use of a titration committee, I found very odd and actually took away even more from the external validity of the study.

I mean, you can argue almost in a way that the titration committee should be the background therapy and part of the label of the trial for the drug, but I just don't think that's a very good idea as well as the short-term nature of the studies.

So I'm glad there's some long-term follow-up studies for cardiovascular safety.

DR. COOKE: David Cooke. I voted yes. I think the reason for that is simply that the data met the primary outcome for efficacy across each of the trials.

Again, with that, there weren't any safety

concerns that were uncovered. I think, with regard to which population it should be approved for, I am in favor of it being approved for all of the groups that were studied, those that are both insulin- and GLP-1-naïve, as well as those who's been on insulin or a GLP-1.

I would agree that it's a little less clear how many patients early on might be initiated on the combination product who have been naïve to both insulin and GLP-1.

But I think that's something that ultimately will be determined over time as we learn more about -- particularly through secondary outcome data that looked promising in these trials, things like controlling weight gain, either inducing weight loss or controlling weight gain, as well as ultimately the durability of effect of this combination agent compared to even insulin, where the dose continues to need to go up over time.

I think that sort of information will be very valuable, although I would say that I don't feel that there are additional post-marketing

studies that should be required.

I think we've got enough data to say that the combination is both safe and efficacious to allow for treatment at this time.

DR. BUDNITZ: Dan Budnitz. I voted yes because, even if we just consider patients already on both agents, just the simplicity and reduced needle sticks from that significant population is a significant population that can benefit.

I think the main risk, other than what folks mentioned before, is really just a risk of a potential loss of opportunity of patients that might be treated with two agents that could be optimally managed by one if it's initiated in naïve patients.

Because it's a fixed GLP-1 insulin ratio, there might be, again, some more optimal combination for an individual patient that could be determined if the two drugs were started independently first.

Then the final point is just to reduce errors and confusions. I would strongly suggest

some sort of unit to be placed on the pen and in the materials so it's not a unitless number that has complications with computerized order entry and with other folks who might not prescribe the drug.

DR. BURMAN: Ken Burman. I voted yes. It would seem most appropriate to utilize this combination agent in uncontrolled type 2 diabetic patients who are already taking basal insulin or a GLP-1 agonist.

It would be difficult to know if a patient requires the combination agent if they were only taking oral agents and was started on the combination.

We have discussed the issues of possible loss of glucose control when first starting the agent in a patient already taking long-acting insulin.

A combination product in general is a double-edged sword. There are advantages and disadvantages. The advantages, obviously, include compliance by patient, decreased patient cost, and injections.

On the other hand, it's difficult to know if each of the agents works effectively. I think, in this study, they seem to work effectively and I think the use of a combination agent is appropriate.

There are multiple issues as we've all discussed. I will not go over all of them, but they relate to the incremental dosing schedule, the difficulty switching, regimens, possible medication error, cap of 50 units of insulin given, missing data, to just name a few.

The central issues in my mind are: Is the combination needed in the healthcare armamentarium to treat uncontrolled diabetes mellitus? My answer is yes.

Do the issues raised such as inflexible dosing and applicability of clinical trials allow for approval of the product? I think the answer is yes.

Do the benefits on A1c outweigh the possible adverse effects of the combination agent and are the clinical trial data relevant? I think the

answer to both is probably yes. And I think there is a need for such an agent.

I would note several caveats. Patients who may require more than 50 units of the degludec a day, obviously, may not qualify or be eligible for this.

Something that we haven't brought up that Dr. Gough had mentioned in one of his previous publications are that there seems to be a different risk of hypoglycemia and effectiveness in different groups.

So they're different and perhaps better in Asian than non-Asians, if I understood that correctly, and I don't think we talked about that at all.

Patients who require intensification of therapy and have an elevated A1c perhaps at least 8.5-9 percent and may require insulin therapy of relatively high doses rather than combination may not be prime candidates for this agent.

Patients with a personal family history of medullary thyroid cancer or C-cell hyperplasia

obviously don't qualify. And we talked about the possibility that lower doses of liraglutide may not be useful overall.

In summary, I think there are multiple issues with this agent that need to be considered. But overall, if used in an appropriate diabetic population, I think it will be a useful agent to help control hypoglycemia, A1c and diabetes.

DR. SMITH: Thank you. Does the FDA then have any final comments?

DR. GUETTIER: We'd like to thank the committee for their deliberations today. We look forward to seeing you, some of you, tomorrow. Thank you.

Adjournment

DR. SMITH: And I would like to thank the panel members, the FDA for their work in presenting the data and clarifying things, the sponsor for your very helpful presentations and the open public hearing speakers also for your contributions.

Panel members, please take your personal belongings with you as the room is cleaned at the

end of the meeting day even if you're coming back to a meeting here tomorrow.

Please remember to drop off your badge at the registration desk. And we'll now adjourn the meeting. Thank you all.

(Whereupon, at 4:47 p.m., the meeting was adjourned.)