FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC) MEETING

Virtual Meeting

Friday, May 24, 2024

9:00 a.m. to 4:04 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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Consultant Management
Office of Executive Programs, CDER, FDA

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OCP, OTS, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. LOW WANG: Alright, it's the top of the hour, so let's get started.

Good morning and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her e-mail is currently displayed.

Thank you for joining the meeting this morning. My name is Dr. Cecilia Low Wang, and I will be chairing this meeting. I will now call the May 24, 2024 Endocrinologic and Metabolic Drugs Advisory Committee meeting to order. Commander LaToya Bonner is the designated federal officer for this meeting and will begin with introduction.

Introduction of Committee

CDR BONNER: Thank you, Chair.

My name is LaToya Bonner -- good morning to you all -- and I am the designated federal officer for this meeting. When I call your name, please

introduce yourself by stating your name and your affiliation. We will start with the standing EMDAC members.

Dr. Drake?

DR. DRAKE: Matthew Drake. I am an endocrinologist, adult endocrinologist, at the Mayo Clinic in Rochester, Minnesota.

CDR BONNER: Thank you.

Next is Dr. Greevy.

DR. GREEVY: Hi. I'm Robert Greevy. I'm a Professor of Biostatistics at Vanderbilt University.

CDR BONNER: Next is Dr. Kalyani.

DR. KALYANI: Hi. Dr. Rita Kalyani. I'm an adult endocrinologist at Johns Hopkins University in Baltimore.

CDR BONNER: Thank you.

Next is our chair, Dr. Low Wang.

DR. LOW WANG: My name is Cecilia Low Wang. I am a Professor of Medicine and an endocrinologist at the University of Colorado School of Medicine in Aurora, Colorado.

CDR BONNER: Thank you.

And our acting industry representative, Dr. Dutta.

DR. DUTTA: Hi. This is Sandeep Dutta. I'm Vice President, Clinical Pharmacology, Modeling, and Simulation at Amgen.

CDR BONNER: Thank you, sir.

Next, we have our temporary voting members, starting with Dr. Beringer.

DR. BERINGER: I'm Paul Beringer. I'm a Professor of Clinical Pharmacy at the University of Southern California in Los Angeles.

CDR BONNER: Thank you.

Dr. Brittain?

DR. BRITTAIN: Hi. I'm Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases, NIH.

CDR BONNER: Thank you.

Dr. Crandall?

DR. CRANDALL: Hi. I'm Jill Crandall. I'm a Professor of Medicine and Chief of Endocrinology at Albert Einstein College of Medicine in New York.

CDR BONNER: Dr. Nason?

DR. NASON: Good morning. I'm Martha Nason. I'm a biostatistician at the National Institute of Allergy and Infectious Diseases, NIH.

CDR BONNER: Thank you.

Dr. Onumah?

DR. ONUMAH: Good morning. Barbara Onumah. I'm a clinical endocrinologist, a clinical practice in Largo, Maryland.

CDR BONNER: Thank you, ma'am.

Dr. Tibbits? Mr. Tibbits; I'm sorry. He is our patient representative for this meeting.

Mr. Tibbits?

MR. TIBBITS: Hi. I'm Paul Tibbits. I have had type 1 diabetes for 44 years. My professional background, I've been in healthcare policy, communications, and advocacy for about 25 years.

CDR BONNER: Thank you, sir.

And Dr. Weber?

DR. WEBER: Good morning. This is Tom Weber. I'm an adult endocrinologist at Duke University Medical Center in Durham, North

Carolina.

CDR BONNER: Thank you, sir.

Now, we will introduce to you our FDA participants, starting with Dr. Yanoff.

DR. YANOFF: Good morning. I'm Lisa Yanoff. I'm the Deputy Office Director in OND for the Office of Cardiology, Hematology, Endocrinology, and Nephrology.

CDR BONNER: Thank you.

Next is Dr. Archdeacon.

DR. ARCHDEACON: Good morning. I'm Patrick Archdeacon, Deputy Director, Division of Diabetes, Lipid Disorders, and Obesity.

CDR BONNER: Thank you.

Next is Dr. Nguyen.

DR. NGUYEN: Hi. I'm Michael Nguyen. I am the Clinical Team Lead in the Division of Diabetes, Lipid Disorders, and Obesity.

CDR BONNER: Thank you.

Next is Dr. Pucino.

DR. PUCINO: Frank Pucino, Clinical Reviewer from the Division of Diabetes, Lipid Disorders, and

Obesity.

CDR BONNER: Thank you.

Dr. Kenna?

DR. KENNA: Leslie Kenna, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology.

CDR BONNER: Next is Dr. Crackel.

DR. CRACKEL: Roberto Crackel, Mathematical Statistician with the Division of Biometrics II in the Office of Biostatistics.

CDR BONNER: Next is Dr. Song.

DR. SONG: Dr. Jaejoon Song. I'm a Safety Statistical Reviewer, Division of Biometrics VII, Office of Biostatistics.

CDR BONNER: Thank you.

Next is Dr. Dahmane?

DR. DAHMANE: Good morning. My name is Elyes Dahmane, Pharmacometrics Reviewer, Division of Pharmacometrics, Office of Clinical Pharmacology.

CDR BONNER: Thank you. That concludes our introduction. I'll hand the meeting back over to

our chair.

Dr. Low Wang?

DR. LOW WANG: Thank you, Commander Bonner.

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

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from

discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Commander Bonner will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you, ma'am. LaToya 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, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that that agency's need for a special government employee's services outweighs their 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 the committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of

their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimonies; contracts, grants, CRADAs; teaching, speaking, writing; patents, royalties; and primary employment.

Today's agenda involves discussion of the safety and efficacy of biologics license application, BLA, 761326 for NNC0148-0287 injection, insulin icodec, a long-acting insulin analog product, submitted by Nova Nordisk. The proposed indication is to improve glycemic control in adults with diabetes mellitus. This is a particular matters meeting during which specific matters related to Novo Nordisk's BLA 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. Sandeep Dutta is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Dutta's role at this meeting is to represent industry in general and not any particular company. Dr. Dutta 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. I will now turn the meeting back

over to our chair.

Dr. Low Wang?

DR. LOW WANG: Thank you, Commander Bonner.

We will now proceed with FDA introductory remarks from Dr. Michael Nguyen.

FDA Introductory Remarks - Michael Nguyen

DR. NGUYEN: Good morning. My name is Michael Nguyen, and I'm the Clinical Team Lead for this application, and I will provide the introductory remarks for this advisory committee meeting. The objective of the AC meeting is to discuss the benefits and risks of insulin icodec, a once-weekly insulin analog product, for the proposed indication to improve glycemic control in adult patients with diabetes mellitus.

There are two main types of diabetes mellitus, type 1 and type 2. Type 1 diabetes is characterized by autoimmune destruction of pancreatic beta cells, loss of insulin secretion, and the requirement for lifelong administration of exogenous insulin, whereas type 2 diabetes is characterized by insulin resistance and inadequate

insulin production, and is treated with many different types of medications, including insulin. Because type 1 and type 2 are distinct conditions with distinct pathogenic mechanisms, responses to an intervention in one form of diabetes does not necessarily predict or correspond with responses to the same intervention in the other. The focus of this meeting will be the safety and efficacy of insulin icodec in patients with type 1 diabetes.

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia and affects an estimated 38 million people in the United States. Type 1 diabetes accounts for 5 to 10 of diagnosed cases. The management of type 1 diabetes requires lifelong insulin therapy, either with continuous subcutaneous insulin infusions or with multiple daily insulin injections, consisting of a bolus and basal insulin.

Maintaining normal glycemia, defined as an A1c less than 7 percent, can reduce the risk of diabetic complications. A1c is a biomarker that

reflects the average glucose level in the prior 2 to 3 months. Hypoglycemia is a major limiting factor in achieving glycemic control with exogenous insulin in people with type 1 diabetes.

There is an unmet medical need in basal insulin therapy for type 1 diabetes. In the U.S., about one-third of adults with type 1 are managed with multiple daily insulin injections. An estimated 22 percent of adults with T1D may miss one or more basal insulin doses over any 14-day period, and nonadherence to insulin therapy is a precipitating factor for diabetic complications such as diabetic ketoacidosis.

Current available basal insulin products are administered once to twice daily. Insulin icodec is a long-acting human insulin analog intended for once-weekly administration. When used for the management of type 2, insulin icodec would reduce a total number of injections from 7 to one per week among patients using basal insulin dosing only. When used for the management of type 1, insulin icodec would reduce the total number of insulin

injections from 28 to 22 per week on average. It is not known whether a once-weekly basal insulin such as insulin icodec would improve adherence and/or glycemic control in patients with type 1.

In December 2020, an end of phase 2 meeting was held with the applicant. During this meeting, FDA noted that the clinical pharmacology results from the study in patients with type 1 revealed that the glucose lowering effect of insulin icodec was not constant across the dosing period when it was dosed weekly. FDA advised that insulin icodec may not be ideally suited for use as a once-weekly product, and that an insulin regimen that included insulin icodec might lead to more hypoglycemia, more frequent bolus insulin adjustments, and less glycemic control.

In this meeting, FDA also agreed with an active comparator, open-label study design for insulin icodec to demonstrate efficacy in adults with type 1, with the primary endpoint of A1c at 6 months. This study later became known as ONWARDS 6. FDA also noted that meeting this

prespecified noninferiority margin would not be sufficient to establish a favorable benefit-risk profile because the risk of hypoglycemia would also be taken into consideration.

FDA recommended that the phase 3 T1D study, ONWARDS 6, include a third arm to evaluate insulin icodec, dosed twice weekly, assess potential improvements in diabetes satisfaction to offset any potential worse glycemic profile and assess the potential need for additional bolus dose adjustments.

Key issues. Insulin icodec is a proposed long-acting insulin analog that if administered once weekly reduces the number of basal insulin injections compared to available daily basal products. It does not have a constant time action profile throughout the dosing interval. The central application finding was that insulin icodec was noninferior to insulin degludec in improving glycemic control, as measured by A1c, but had an increased risk of level 2 or 3 hypoglycemia. This meant that insulin icodec met the regulatory

approval standard for efficacy but is associated with a worse safety profile than once-daily insulin degludec.

The applicant proposed several mitigation strategies to address the greater risk of hypoglycemia. I will preview the main options here and allow subsequent FDA presenters to share further details. First, indicate insulin icodec only for patients with low glycemic variability. Second, limit the use of insulin icodec to certain patients, for example, adults using continuous glucose monitoring devices. Third, label alternative bolus insulin dosing strategies.

Discussion points for the committee. In adults with type 1 diabetes, discuss the benefits of insulin icodec and the risk of hypoglycemia. Discuss the role of continuous glucose monitoring devices and measures of glycemic variability with respect to the risk of hypoglycemia in patients using insulin icodec. Discuss the proposed dosing and titration regimen and the extent to which the modeling data support alternative dosing

strategies. Discuss the role of insulin icodec in the context of the available treatment armamentarium to improve glycemic control.

Voting question for the committee. Based on the available data, has the applicant demonstrated that the benefits of insulin icodec outweigh its risks for improving glycemic control in adults with type 1 diabetes? If yes, explain your rationale. Comment on any risk mitigation measures you believe would be necessary to ensure that the benefits outweigh the risks. If no, explain your rationale and comment on any additional data that could be provided to demonstrate that the benefits outweigh the risks. This completes my presentation.

DR. LOW WANG: Thank you, Dr. Nguyen, for that introduction and articulation of the key issues.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure that such transparency is present at the advisory committee meeting, FDA believes that it's

important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentations by Novo Nordisk.

Applicant Presentation - Shawn Hoskin

MR. HOSKIN: Members of the committee, FDA colleagues, good morning. My name is Shawn Hoskin,

Executive Director of Regulatory Affairs at Novo Nordisk. Thank you for the opportunity to present the data supporting use of the insulin icodec, a long-acting human insulin analog to be administered once weekly for the treatment of adults with diabetes mellitus.

Insulin icodec represents the continued evolution of insulin therapy and was specifically designed to reduce the burden of insulin treatment and better meet the needs of people with diabetes. For decades, innovation in insulin development has been guided by the need to reduce patient burden and the frequency of insulin injections. Insulin icodec was designed to retain all the well-known actions of human insulin, with a PK/PD profile that would be suitable for patients to cover their basal insulin requirements with a single once-weekly injection.

The icodec molecule consists of a modified insulin peptide backbone with a fatty acid side chain. It binds strongly and reversibly to albumin, slowing clearance and creating a depot of

icodec in the circulation and interstitial tissues. The albumin bound icodec itself is essentially inactive; however, active insulin icodec is slowly and continuously released from this depot. These properties and receptor binding characteristics contribute to sustained glucose lowering with once-weekly dosing in both type 2 and type 1 diabetes.

The PK/PD properties of insulin icodec are maintained across a variety of patient characteristics. The peak-to-trough ratio of insulin icodec across 1 week is similar to the ratio of other basal insulins over one day.

Insulin icodec has been submitted for review and approval to a number of health authorities around the world. To date, icodec has been approved in Canada and Switzerland, and recently received approval in Europe for the treatment of diabetes in adults with both type 1 and type 2 diabetes. If approved in the United States, insulin icodec would be the first once-weekly basal insulin for people with diabetes.

Insulin icodec was evaluated in the ONWARDS development program, which included six phase 3 randomized, parallel group, multicenter, multinational trials, comparing the efficacy and safety of insulin icodec versus an active control across a diverse population of people with diabetes. As described by FDA, today's meeting is focused solely on the benefit-risk of insulin icodec for the treatment of people with type 1 diabetes; however, because the full data package augments our knowledge of efficacy and safety, we will briefly summarize the results from trials in people with type 2 diabetes.

Evidence from the ONWARDS 1 to 5 trials demonstrates that once-weekly insulin icodec is a safe and effective long-acting insulin for people with type 2 diabetes. In all studies, icodec met the primary objective, demonstrating noninferiority to daily basal insulin for change in HbA1c with reductions sustained for 52 weeks. Continuous glucose monitoring, or CGM data, support that icodec is comparable to daily basal insulin for

time-in-target glucose range.

The general safety profile is consistent with the well-known profile of daily basal insulin. The absolute event rates of severe or clinically significant hypoglycemic episodes were low, and there was no excess of level 3 hypoglycemic episodes with insulin icodec. The totality of evidence across all ONWARDS studies in people with type 2 diabetes consistently demonstrates a favorable benefit-risk for once-weekly insulin icodec. Data from the ONWARDS 6 trial supports that once-weekly insulin icodec can be used safely and effectively in adults with type 1 diabetes.

Insulin icodec met the primary endpoint, demonstrating noninferior reductions in HbA1c compared to insulin degludec, and the CGM measured time-in-target range was not clinically different. The general safety profile of insulin icodec was consistent with insulin degludec, with the exception of hypoglycemic episodes.

Today, we are here to discuss the benefit-risk of insulin icodec in adults with

type 1 diabetes. As we will demonstrate, the clinical trial supports that episodes of hypoglycemia occurring with insulin icodec in participants with type 1 diabetes are no different than those occurring with insulin degludec. When episodes did occur with insulin icodec, they were successfully managed using the same instructions and methods used for insulin degludec.

The mean duration of hypoglycemia was not longer with weekly insulin icodec compared with daily insulin degludec. No characteristics were identified to predict for a difference in relative hypoglycemia risk with insulin icodec compared to other basal insulins. Consistent with clinical practice and in line with recommendations, healthcare professionals will use their clinical judgment to individualize care.

To help guide individualized care, information on hypoglycemia risk factors and the pharmacodynamic profile of insulin icodec will be shared with physicians. This includes communicating that the greatest glucose lowering

effect with icodec occurs on days 2 to 4 after injection. We have also proposed limitations of use in patients known to have increased hypoglycemia risk. The totality of evidence supports that healthcare professionals will be able to use icodec with a favorable benefit-to-risk profile for adults with type 1 diabetes.

Icodec will be available in a U-700 prefilled insulin pen injector. The pen will deliver insulin icodec in 10-unit increments with a maximum single injection of 700 units. It is important to understand that the concentration of insulin icodec is 7 times the concentration of approved basal insulin analogs; therefore, the volume of icodec injected weekly is the same as the volume injected daily with a currently available basal insulin.

Here is the agenda for the remainder of today's presentation. We also have additional experts with us today. All outside experts have been compensated for their time and travel to today's meeting. Thank you. I'll now turn the

presentation over to Dr. Lingvay.

Applicant Presentation - Ildiko Lingvay

DR. LINGVAY: Thank you, and good morning. My name is Ildiko Lingvay, and I'm a Professor of Medicine at University of Texas Southwestern, but I have been caring for patients with diabetes for more than 20 years. As an investigator in 4 of the 6 ONWARDS trials and two of the phase 2 trials, I have experienced treating patients with once-weekly insulin icodec. I will review the unmet need for a once-weekly basal insulin for people with type 1 and type 2 diabetes.

Insulin has an important role in the treatment of people with diabetes. For people with type 1 diabetes, it is the life-saving treatment. For people with type 2 diabetes, it is one of the most effective glucose lowering interventions. All people with type 1 diabetes and nearly a third of people with type 2 diabetes are treated with insulin. That is approximately 1.7 million people with type 1 diabetes and 7.4 million people with type 2 diabetes in the U.S. alone who use insulin

every day.

Over the last several decades, we have seen important advances in insulin treatment, yet many patients still have significant hesitations and concerns about insulin therapy. Insulin is one of the most burdensome treatments for diabetes. Barriers to insulin treatment include fear of injections; inconvenience; the associated practicalities; the social stigma.

Just one such example is the added complexity and inconvenience insulin treatment imposes should one need to travel, from packing all the supplies; the embarrassment of the extra scrutiny in the security line; curious glances of onlookers, sharps disposal and the risk of losing or breaking the insulin. It is not an overstatement that insulin therapy is burdensome and impacts quality of life.

This sentiment regarding insulin therapy has important consequences. First, it leads to delays in initiating insulin in people with type 2 diabetes who would benefit from this treatment.

Insulin initiation is commonly delayed by several years. Once initiated, adherence is suboptimal, limiting insulin for potential to control glycemia. Nonadherence with insulin, whether measured by fill rates or patient questionnaires, is high.

Over half of people with type 1 and type 2 diabetes meet criteria for nonadherence. In a study that evaluated 507 people with type 1 and type 2 diabetes, those with low adherence were more likely to report forgetfulness, time required for insulin administration, and embarrassment as barriers to insulin use.

Missing insulin injections has multiple consequences. First, it impacts the ability to achieve glycemic control. In this prospective real-life study of adults with type 1 diabetes receiving insulin injections, continuous glucose monitoring data was used to evaluate the impact of missed doses on glycemic outcomes. Over a 14-day period, 17.7 percent missed one dose of basal insulin and 3.6 percent missed 2 doses. A single missed basal insulin dose was associated with a

reduced time-in-target glucose range of 2.6 percent and two missed basal insulin doses resulted in a 5.3 percent reduction. These data highlight that missed injections can have a considerable impact on glycemic control.

Low insulin adherence has additional documented consequences. In this real-world data from a large commercial healthcare database, insulin nonadherence, defined as less than 80 percent proportion of days covered, was associated with increased healthcare utilization. Nonadherence was associated with a higher number of hospitalizations, days spent in the hospital, and number of emergency room visits. Both diabetes related and all-cause resource utilization were higher in those meeting criteria for nonadherence.

Nonadherence to basal insulin therapy was also associated with a 23 percent increase in the probability of an acute diabetes complication over the three-year follow-up period. Low adherence is also the most common cause for recurrent diabetic ketoacidosis. This retrospective study found that

the odds of recurrent DKA was 26 times higher among those with poor adherence to insulin, even when other known factors were accounted for.

Studies show that a lower frequency of administration of injectable therapies improves adherence. In this observational, retrospective, real-world study in adults with type 2 diabetes, treatment with once-weekly injectable GLP-1 was associated with significantly higher persistence and adherence when compared to daily GLP-1 regimens. The median time on therapy was 64 days longer within the 12-month study compared with daily injections. Adherence to therapy was 35 percent higher at 12 months among patients receiving weekly injectables.

It is not surprising that therapies with less frequent administrations improve adherence and persistence. In fact, this has been shown in multiple other therapeutic areas as well. Based on existing information, as well as my clinical experience, once-weekly insulin has the potential to reduce barriers to insulin initiation, minimize

treatment burden, improve quality of life, and increase treatment adherence and persistence. Improved adherence is expected to translate to better glycemic control, fewer diabetes related complications, and lower healthcare utilization and healthcare costs. Thank you. I will now turn the presentation over to Dr. Gough.

Applicant Presentation - Stephen Gough

DR. GOUGH: Good morning. I am Stephen Gough, Global Chief Medical Officer of Novo Nordisk and a registered clinical endocrinologist. I'm pleased to be here today to provide an overview of the ONWARDS development program and discuss icodec dosing.

The ONWARDS development program includes six phase 3 randomized parallel group, multicenter, multinational trials, comparing the efficacy and safety of insulin icodec versus an active control. The five studies in people with type 2 diabetes, ONWARDS 1 through to 5, support use in an insulin-naive population, the odd number studies, as well as patients with prior basal insulin, the

even number studies.

ONWARDS 6 evaluated basal bolus therapy in people with type 1 diabetes. ONWARDS 6 included a 26-week main phase with prespecified assessments of efficacy, safety, and hypoglycemia. Long-term safety was further evaluated in participants who completed the main phase of the study and continued into the 26-week extension. Please note, we chose insulin degludec as the active comparator, as it is recognized to result in less severe hypoglycemia than insulin glargine.

The ONWARDS trials incorporated dosing algorithms for participants who were new to insulin and for those who transitioned from daily basal insulin. Beginning with type 2 diabetes, participants who were insulin naive received a starting dose of 70 units of insulin icodec. For participants who used daily basal insulin at randomization, the first icodec dose was 1.5 times the weekly equivalent of their previous daily dose to more rapidly achieved steady state due to the long half-life. The second dose was 7 times the

previous daily basal dose.

Dosing in type 1 diabetes additionally considered baseline A1c and basal insulin regimen. For participants with an A1c of less than 8 percent, icodec dosing was the same as for type 2 diabetes. Participants who previously used insulin glargine U-300, or twice daily basal insulin, also followed this algorithm. When baseline A1c was greater than 8 percent, the icodec starting dose was twice the weekly equivalent of the previous basal dose.

Subsequent icodec dose titration was based on the self-monitoring of blood glucose values. Investigators adjusted the icodec dose weekly to achieve target glucose values. In type 2 diabetes, dose adjustments considered both the lowest and mean blood glucose values. In type 1 diabetes, dose adjustments were guided by the lowest value between dose measured on the day of titration and the 2 days before. The dose algorithm for the daily basal insulin comparator arms was also prespecified. The primary hypothesis across all

trials was that the change in A1c with insulin icodec was noninferior to daily insulin comparator.

Additional secondary endpoints, including multiple measures of glycemic control, were collected. Some of these values were derived from continuous glucose monitoring data. This allowed us to compare the time spent within the target glucose range and the amount of time below 54 milligrams per deciliter and above the target range in the insulin icodec group versus the comparator groups.

To collect these data, we used continuous glucose monitoring, or CGM, to augment the more traditional glycemic efficacy and safety assessments. CGM provides accurate glucose values and trends throughout the day and night. ONWARDS 1, 2, and 4 included CGM in the last 4 weeks of the planned treatment period. Participants and investigators were blinded to these data. In ONWARDS 6, which evaluated patients with type 1 diabetes, CGM data were collected throughout the entire trial. Participants and

investigators were not blinded to these data.

A weekly insulin naturally raises concerns about hypoglycemia, especially in type 1 diabetes where counter regulatory mechanisms may be dysfunctional; therefore, as part of our thorough safety evaluation in participants with type 1 diabetes, we considered the potential for more frequent or prolonged hypoglycemic episodes that might prove challenging for participants to manage by themselves. We also looked at the timing of events with a particular focus on the relationship to dosing. Furthermore, we investigated risk factors associated with hypoglycemia.

We systematically examined hypoglycemia episodes across the ONWARDS trials. These are classified by severity level. Level 1 is an alert value defined by glucose values between 54 and 70 milligrams per deciliter, while level 2 is a clinically significant event defined as a plasma glucose level below 54 milligrams per deciliter. Level 3 events are categorized as severe and include cognitive impairment and/or the need for

assistance from another person.

Prespecified analyses were conducted for combined level 2 and level 3 hypoglycemia. In addition, we performed a post hoc analysis of clinically significant level 2 hypoglycemic episodes using CGM-based data. CGM-based hypoglycemia detection and reporting is well established in current clinical guidelines and regulatory guidance. This method provides a more objective assessment of hypoglycemia, as it is based on extensive data with 5-minute interval glucose values; therefore, the results are not impacted by the frequency of measuring nor manual self-reporting by the participant, which is required for the prespecified SMBG-based approach. For consistency, the same CGM device was used across the ONWARDS studies.

As shown in the briefing document, the enrolled populations were generally representative of the diverse diabetes population as seen in clinical practice. These baseline demographics and characteristics were balanced between the treatment

groups within each population, and more than 94 percent of participants randomized to receive icodec completed the main trial period.

Baseline characteristics were well balanced across treatment groups and reflect the populations targeted for each trial. More than 30 percent had mild to moderate renal impairment. Most participants with type 1 diabetes had an A1c of less than 8 percent, and more than 70 percent of participants in ONWARDS 6 had a diabetes duration of more than 10 years.

Thank you. I will now turn the presentation over to Dr. Cailleteau.

Applicant Presentation - Roman Cailleteau

DR. CAILLETEAU: Thank you, and good morning. My name is Roman Cailleteau, and I'm a Senior Medical Director at Novo Nordisk. I will start by summarizing the general safety data gathered in the phase 3 program, which supports that the overall safety profile of weekly insulin icodec is similar to the well-established profile of daily basal insulins.

The safety profile of insulin icodec has been evaluated in a cohort of more than 2,100 participants enrolled in the phase 3 program. While the focus of today's meeting is on type 1 diabetes, safety data gathered across the entire population in the ONWARDS studies support the overall benefit-risk profile of insulin icodec.

Results from the ONWARDS program demonstrate that the overall safety profile of icodec is similar to the well-established profile of daily basal insulin. No unexpected findings or unacceptable risks have been identified. The majority of events in both groups were non-serious, mild, and investigator judged as unlikely to be related to trial product and resolved over time. In participants with type 1 diabetes, a similar pattern of events was observed with the exception of hypoglycemia. This data can be found in our briefing document.

I will now briefly review the efficacy results in people with type 2 diabetes. In all studies of people with type 2 diabetes, once-weekly

insulin icodec met the primary objective, demonstrating noninferiority to daily basal insulin or change in A1c. Shown here, insulin icodec is in blue and the basal insulin comparators are in shades of gray. Reductions in A1c among participants receiving insulin icodec were consistent across all populations, including those who were insulin naive at baseline and those who were switched to insulin icodec from daily basal insulin. Please note that throughout the core presentation, we only show p values for prespecified, alpha protected analysis.

Next, we evaluated time within the target glucose range, as measured by CGM. On this graph, insulin-naive participants receiving icodec, shown in the bar to the left, spent more than 70 percent of time in range. This figure corresponds to the recommended target in international treatment guidelines.

Participants who switched to icodec from daily basal insulin, the center bars, and those on a basal bolus regimen, to the right, spent 63 and

67 percent of the time within range. In each case, participants on a daily basal insulin experienced comparable efficacy. In all trials where CGM was used, time below range with icodec was aligned with daily basal insulins. Participants receiving insulin icodec spent 0.7 percent of the time or less with glucose below 54 milligram per deciliter.

Let me now provide an overview of the hypoglycemia episodes in the type 2 diabetes population. A weekly insulin naturally raises concerns about hypoglycemia, so we carefully monitored hypoglycemia in all clinical trials. This table presents a proportion of participants with level 2 or 3 hypoglycemic episodes. Overall, the majority of participants did not experience hypoglycemic episodes, with the exception of those receiving bolus insulin in ONWARDS 4.

The proportion of insulin-naive and basal-switch participants experiencing a level 2 or 3 hypoglycemic episodes was numerically higher, which is in icodec compared to daily basal insulins. In these two populations, only one

participant reported a single level 3 hypoglycemic episodes. Not surprisingly, among those also taking bolus insulin in ONWARDS 4, the proportion was higher than other ONWARDS trial. Notably, the proportion experiencing level 2 or 3 hypoglycemic episodes were similar between treatment groups.

The event rate differences are reflected by the rate ratio numbers of level 2 or 3 hypoglycemic episodes per patient year of exposure. Insulin naive and prior basal insulin populations show a higher rate with insulin icodec compared to daily basal insulin. These differences were driven by level 2 events. Importantly, the absolute events rates were low in both treatment groups, with individuals experiencing less than one episode per patient year.

In summary, evidence from five randomized control studies demonstrates that once-weekly subcutaneous administration of insulin icodec provides effective glycemic control in people with type 2 diabetes. In terms of hypoglycemia risk, absolute events rates of severe or clinically

significant hypoglycemic episodes were low, and there was no excess of level 3 episodes with insulin icodec. Hypoglycemic episodes with icodec were manageable by participants consistent with daily basal insulin products. Finally, the titration algorithm provided safe and efficacious dosing of insulin icodec.

Thank you. I will now turn the presentation over to Dr. Gough.

Applicant Presentation - Stephen Gough

DR. GOUGH: Thank you. I will now present the data demonstrating that a once-weekly subcutaneous injection of insulin icodec provides safe and effective glycemic control in participants with type 1 diabetes. First, let me discuss the efficacy results.

In ONWARDS 6, insulin icodec provided noninferior reductions in A1c as compared to daily basal insulin, in this case insulin degludec. As shown on the left, the estimated treatment difference, the change in A1c, was 0.05, meeting the prespecified noninferiority criterion. The

figure on the right shows comparable decreases in A1c from baseline through to week 26 among all treated participants. Overall, these data show that weekly insulin icodec behaves similarly to insulin degludec for A1c reduction in type 1 diabetes.

CGM data collected during weeks 22 to 26 of the main treatment period are shown here. The time spent within the target range of 70 to 180 milligrams per deciliter was approximately 60 percent with both insulin icodec and insulin degludec, and time spent below 54 milligrams per deciliter was 1 percent in the insulin icodec arm, at the threshold of the international guidelines of less than 1 percent and comparable to the daily insulin control group. Time spent below 70 milligrams per deciliter was less than 4 percent in both treatment groups, meeting treatment guidance targets. These data support similar glycemic effects of weekly icodec and daily insulin degludec.

Furthermore, evidence from ONWARDS 6

demonstrates that the dosing algorithm for insulin icodec is effective in people with type 1 diabetes. Presented here is mean self-monitored fasting blood glucose throughout the main trial period. Participants receiving insulin icodec were able to effectively titrate to target on a weekly basis and achieve fasting glucose levels comparable to those in the insulin degludec group.

Mean CGM data during weeks 22 to 26 show the day-to-day and within-day fluctuations in mean glucose levels for insulin icodec and daily insulin degludec. Focusing on weekly insulin icodec in blue, the majority of glucose values were within the target range. Day 1 represents the day of icodec dosing. Overall, glucose values were generally lower on days 2 through to 4 when compared to day 6 through to 7.

Next, I'll provide an overview of the hypoglycemia in people with type 1 diabetes. The proportions of participants who reported hypoglycemic episodes by classification level among participants with type 1 diabetes are presented

here. As expected, almost everyone in the study experienced a level 1 episode. A higher proportion of participants in the insulin icodec group, 85 percent, reported level 2 episodes compared with 76 percent of participants receiving daily insulin degludec; however, this did not translate into a higher proportion reporting a level 3 episode, as 3 percent corresponding to 9 participants in each group reported a severe episode.

Level 2 or 3 hypoglycemic episodes are presented here by event rates and rate ratios for the ONWARDS 6 trial. The numbers of events and the rate ratios were higher among participants receiving insulin icodec compared to insulin degludec. This difference was primarily driven by level 2 episodes. For level 3 episodes, 70 percent of the 47 total hypoglycemic episodes observed with insulin icodec occurred in a single participant who experienced 33 episodes. Thus, the higher rate of level 3 episodes is driven by this one participant.

Shown here are the number and proportion of participants in each treatment group who reported

various numbers of level 3 hypoglycemic episodes during the ONWARDS 6 study. One participant in the icodec group and one in the insulin degludec group reported five or more level 3 episodes. Importantly, the individual treated with icodec who experienced the 33 episodes did not withdraw and remained in the study through the extension phase.

To illustrate the management of this participant during the course of the trial, shown on the next slide is the timing of level 3 episodes and the changes to the basal insulin dose. Shown here is total weekly basal insulin dose on the Y-axis with time on the X-axis. Each level 3 episode experienced by the participant is depicted by a vertical line.

As illustrated, the majority of the episodes occurred during the first 8 weeks. The basal insulin dose shown by the blue line was increased despite the occurrence of several level 3 episodes. After reducing the basal insulin by a third by week 13, only one additional level 3 episode occurred. Importantly, this example supports that

insulin icodec, similar to other basal insulins, needs to be individualized to avoid hypoglycemia; for example, by adjusting the insulin dose or considering hypoglycemic risks associated with the individual's characteristics, such as high glycemic variability.

When hypoglycemia did occur, the same management approaches were used for people in the insulin icodec and the daily insulin degludec groups. To illustrate this point, the management of severe level 3 hypoglycemic episodes in the ONWARDS 6 study is summarized here.

As I have shown you, more episodes occurred with icodec than with insulin degludec; however, the proportion that required medical assistance was comparable in both groups, and most participants in both treatment groups were treated with oral intake alone for these severe episodes. Similar proportions of participants were treated with parenteral glucose in both treatment groups, while 3 episodes in 2 participants in the icodec group were treated with glucagon.

To better understand the increased incidence of hypoglycemia with insulin icodec versus insulin degludec, we evaluated the temporal pattern over the course of the dosing interval. Here, all episodes over 26 weeks averaged within the 7-day dosing interval are displayed by the day on which they occurred, shown as the proportion of the total weekly events. Day 1 is the day on which insulin icodec was administered. A uniform distribution over 7 days would be 14 percent in each day.

The risk of severe level 3, or clinically significant level 2 hypoglycemia, was highest on days 2 to 4 after icodec administration. This predictable pattern is in line with the insulin icodec pharmacodynamic profile as shown earlier by CGM measured glucose over the week.

As presented in the introduction, hypoglycemia was also evaluated using CGM-based data. This analysis showed a more reassuring rate ratio for level 2 hypoglycemic episodes compared to self-monitored blood glucose. In line with current clinical guidelines and regulatory guidance, CGM

provides an unbiased perspective that is most representative of actual blood levels. This more objective assessment shows a rate ratio for level 2 hypoglycemia of 1.38 that was lower than the value of 1.88 based on self-reported episodes of hypoglycemia.

Next, we evaluated the duration of hypoglycemic episodes using the continuous glucose monitoring data from weeks 22 to 26 in participants with type 1 diabetes. In this analysis, a CGM level 2 hypoglycemic episode is defined when interstitial glucose is below 54 milligrams per deciliter for more than 15 minutes. The duration of the episode is calculated as the time spent with glucose below 70 milligrams per deciliter. The distribution of episode durations was comparable to insulin icodec and insulin degludec, with most episodes in both treatment groups lasting 30 to 90 minutes.

As an additional means of understanding the risk of hypoglycemia and developing strategies to optimize icodec's benefit-risk, we evaluated the

potential contribution of specific participant characteristics to the risk of hypoglycemia. These comprehensive analyses conclude that no participant characteristics predict for a difference in relative risk of hypoglycemia between insulin icodec and insulin degludec. In addition, no subgroups were identified with a differential benefit-risk profile with icodec; however, some of the subgroups demonstrated a lower absolute risk of hypoglycemia, which can benefit physicians when managing hypoglycemia risk.

First, we analyzed data from both ONWARDS 6 treatment arms to better understand whether any specific characteristics could uniquely predict risk of hypoglycemia among people on insulin icodec. As detailed in the briefing document, we evaluated a number of parameters and identified no unique risk factor for insulin icodec.

Presented in this forest plot are the rate ratios of hypoglycemia by key baseline characteristics, including BMI, diabetes duration, and glycemic variability within each treatment arm.

Among the parameters that we assessed, glycemic variability derived from CGM data had the greatest impact on hypoglycemia risk in both treatment arms, with lower variability associated with the lowest absolute risk. These results are consistent with those reported in peer-reviewed literature for other forms of insulin.

Importantly, all risk factors affecting the risk of hypoglycemia impacted insulin icodec and insulin degludec equivalently. Thus, no subgroups for insulin icodec were identified who had a differential hypoglycemia risk compared to insulin degludec.

So, how can we use this information to optimize the benefit-risk of icodec in clinical practice? Let's focus first on glycemic variability derived from CGM. As I just showed you, low glycemic variability, defined by ADA guidelines as 36 percent or less, was associated with lower hypoglycemic risk in both treatment arms. As shown to the left, the absolute rate of level 2 or level 3 hypoglycemic episodes was

50 percent lower in the low variability subgroup versus the overall population in both treatment groups. As a result, the rate ratio of hypoglycemia between icodec and degludec remains similar. As illustrated to the right, the lower absolute hypoglycemia rate was associated with similar A1c lowering versus the overall population in both groups.

This knowledge could help prescribers and patients to individualize treatment. For example, if a prescriber were considering using icodec for an individual who has high glycemic variability, this information can be used to help optimize treatment by adjusting the glycemic target or reducing the insulin dose.

Next, ONWARDS 6 established that the dosing regimen for insulin icodec can be used safely and effectively for most people with type 1 diabetes; however, given the PD profile of insulin icodec, a bolus adjustment may optimize the benefit-risk for some people. To better inform how to individualize therapy, we performed modeling to evaluate the

potential impact of adjusting bolus insulin doses. As part of this activity, we considered which information could be used in a clinical setting to reduce the risk of hypoglycemia while maintaining good glycemic control for each individual. We also evaluated which information from this analysis could be most effective for informational materials for prescribers and people considering using insulin icodec.

We performed simulations to predict the impact of alternative bolus insulin dosing strategies. The simulation model considered the pharmacodynamic profile of insulin icodec, degludec, and insulin aspart; meal intake; and behavioral elements associated with a glucose turnover model. This model was adapted from a published model. As detailed in the FDA briefing book, there is alignment of modeled results and the observed results in ONWARDS 6, confirming the predictive value of the model.

Here we have modeled reducing the bolus insulin dose by 30 percent on days 2 to 4 without

changing the basal insulin algorithm. This model accounts for the pharmacodynamic profile of insulin icodec with a maximal effect on days 2 to 4. As shown on the left, the rate of level 2 hypoglycemic episodes is almost 50 percent lower, 13 versus 21 episodes per year of exposure with the bolus dose reduction. This value approximates the 11 episodes per year from the degludec simulation.

This reduced rate of hypoglycemia was achieved with a minor reduction in A1c lowering as illustrated to the right. ONWARDS 6 shows that this modification in bolus dosing would not be necessary for all patients. This information may also help clinicians and patients individualize treatment. For example, if a person with type 1 diabetes were to initiate insulin icodec and was at risk of experiencing excess hypoglycemia, the prescriber could suggest bolus insulin dose reductions on days 2 to 4.

As I've shown you here, and in the briefing document, we identified no unique hypoglycemia risk factor for insulin icodec. This finding indicates

that known hypoglycemia risk mitigation methods used for daily insulins can be applied when prescribing insulin icodec. These include measures such as adjustment of the titration target or dose reductions.

We've provided two examples of how prescribers and patients might use insights on individual glycemic variation and of icodec's pharmacodynamic profile to individualize treatments in specific situations. These examples illustrate that physicians may be able to mitigate and reduce the risk of hypoglycemia in people with type 1 diabetes who would benefit from having a weekly insulin available as a treatment option.

In summary, the data support a positive benefit-risk with insulin icodec, providing safe and effective glycemic control in people with type 1 diabetes. Icodec was noninferior to insulin degludec for reduction in A1c, and the reductions persisted throughout the treatment. No clinically meaningful differences in CGM measured time below target glucose range or time above range were

observed among patients receiving icodec or daily insulin degludec.

Hypoglycemia occurs with insulin icodec, just as with any basal insulin product. In participants with type 1 diabetes, a higher rate of level 2 and 3 hypoglycemia was associated with weekly insulin icodec as compared with insulin degludec, primarily driven by a higher rate of level 2 episodes. Importantly however, the clinical trials demonstrated that hypoglycemic episodes with icodec were manageable by participants using the same instructions and methods used for insulin degludec.

In addition, the mean duration of hypoglycemic episodes was not longer with weekly insulin icodec compared with daily insulin degludec. Reassuringly, knowledge that recognized hypoglycemia risk factors consistently predict the increased episodes, and awareness of the icodec pharmacodynamic profile supports the application of well-known strategies to mitigate the risk of hypoglycemia. Thank you. Let me now give the

lectern back to Dr. Lingvay.

Applicant Presentation - Ildiko Lingvay

DR. LINGVAY: Thank you.

Let me provide my clinical perspective on the potential use of insulin icodec in clinical care. Based on the ONWARDS clinical trial program, I conclude that for people with type 2 diabetes, the benefit-to-risk balance of insulin icodec is undeniably favorable. Insulin icodec provided glycemic control that was noninferior to daily basal insulins with no difference in level 3 hypoglycemia. There was a small imbalance in level 2 hypoglycemia, but the absolute numbers were so low that they are unlikely relevant to clinical practice. In the insulin-naive population, this imbalance amounts to one additional episode of level 2 hypoglycemia for every 6 years or longer of treatment with icodec.

There were no safety concerns identified, however, in the ONWARDS 6 trial, which evaluated insulin icodec in people with type 1 diabetes, the rate of hypoglycemia was significantly higher

compared to insulin degludec. Several points are noteworthy to understand the impact of this finding on clinical care and the benefit-risk balance.

First, the same patient characteristics are associated with a higher risk of hypoglycemia with icodec as with daily basal insulins and are therefore already known to providers. For example, people with a higher glucose variability on CGM, those with history of recurrent or severe hypoglycemia, and hypoglycemia unawareness or multiple comorbidities have a higher risk of hypoglycemia. Providers will have to consider the baseline risk for hypoglycemia when selecting the right candidate for the treatment with weekly insulin.

Second, days 2, 3, and 4 after each weekly injection of icodec are the days with the highest risk of hypoglycemia. This is consistent with icodec's pharmacodynamic profile that has a peak-to-trough ratio of 1.8 over 1 week. Interestingly, the peak to trough of insulin glargine is also 1.8, albeit over 1 day; yet,

practitioners and patients learned how to use glargine safely and effectively.

Knowing icodec's action profile will enable practitioners and patients to proactively make adjustments to treatment, meals, or activity as appropriate to prevent hypoglycemia. Providers and patients will learn how to best use this new insulin just as they learned how to use glargine and all other insulins.

When hypoglycemia did occur in the development program, it is reassuring that the duration and treatment were similar to that with daily insulin. It is also relevant that 97 percent of participants in both groups experienced no level 3 hypoglycemia. When hypoglycemia occurs in clinical practice, further treatment individualization will be applied as it is for all insulins.

Insulin icodec will be a particularly valuable treatment option for people with type 1 diabetes who could benefit from its once-weekly administration. Some examples include individuals

who struggle with therapy adherence; who have recurrent admissions for diabetic ketoacidosis; who rely on caregivers for treatment administration; those institutionalized or in care facilities; those who consider daily basal insulins too burdensome; young adults; or those with unpredictable daily schedules like shift workers.

It is important to note that these special populations were not enrolled in the ONWARDS trials; however, these populations are almost never studied in clinical trials, yet clinicians learn how to individualize insulin therapy to the needs of each patient. Only about 425,000 people in the U.S. continue to use insulin injections rather than an insulin pump. This group is enriched with people who might benefit from a once-weekly insulin.

For people with type 1 diabetes, treatment individualization is the key to the safe use of weekly insulin icodec. Clinical trials are helpful to establish population level safety and efficacy; however, the restrictions and inflexibility on

clinical trials do not reflect clinical practice, where we treat each individual according to their unique situation and needs, including their beliefs, struggles, and personal choices. Providers who treat patients with type 1 diabetes are already familiar with treatment individualization and hypoglycemia management.

The risk of hypoglycemia with insulin icodec treatment can be effectively mitigated using the same general concepts already used in clinical practice. Treatment adjustments commonly made in practice to mitigate hypoglycemia include alterations in titration frequency or increments decreasing insulin dose; relaxing the glycemic target; splitting the insulin dose; modifying daily bolus insulin coverage; or if needed, switching to a different insulin. People with type 1 diabetes who could improve adherence with a weekly insulin or those who desire the convenience of fewer injections should not be denied the option of a weekly insulin.

Every treatment we employ in medicine has

benefits and risks, and the art of medicine is understanding this balance and ensuring that for each individual patient this balance is favorable. With that in mind, this is how I view the balance for insulin icodec.

Icodec is an ideal basal insulin for most of the 7.4 million people with type 2 diabetes in the U.S. who require insulin treatment. Icodec has proven its glucose lowering efficacy and its overall safety in this population while comforting the invaluable benefit of convenience. On the other hand, icodec is a valuable treatment option for some people with type 1 diabetes who still use daily insulin injections. This population will have to be carefully selected to ensure they benefit from a weekly basal insulin administration and do not have a high risk of hypoglycemia.

In clinical practice, the known risk of hypoglycemia on days 2 through 4 of administration can be safely managed at an individual patient level by active monitoring and appropriate adjustments to therapy and lifestyle. Ultimately,

icodec's benefit is the reduced treatment burden, a benefit of 313 fewer injections per year.

I wanted to end by sharing the sentiments of the people who participated at my site in the icodec clinical trials and were randomized to the icodec arm. They were unanimously disheartened at the end of their respective time in the clinical trial when they had to switch back to a daily basal insulin. They made me promise that I will do everything in my power to help make this insulin available to them again. This is why I stand here today. Thank you. I will now turn the presentation to the sponsor to conclude.

Applicant Presentation - Stephen Gough

DR. GOUGH: Thank you, Dr. Lingvay.

I will now conclude the presentation. Starting with type 2 diabetes, evidence from five randomized-controlled trials demonstrates that the benefits of once-weekly subcutaneous injection of insulin icodec outweigh the potential risks in people with type 2 diabetes. In all studies, once-weekly insulin icodec met the primary

objective, demonstrating noninferiority to daily basal insulin for change in A1c. The A1c and blood glucose benefits were sustained within target ranges. Importantly, the safety profile of icodec was similar to the well-established profile of daily basal insulin, and there was a low absolute event rate of hypoglycemic episodes.

Moving now to type 1 diabetes, insulin icodec demonstrated noninferior reductions in A1c compared to insulin degludec. The proportion of participants achieving A1c targets and the time spent within target glucose range was similar between insulin icodec and insulin degludec, and the overall safety profile was consistent with insulin degludec.

Hypoglycemia with insulin icodec in participants with type 1 diabetes did occur at a higher rate compared with insulin degludec, and we acknowledge the importance of this finding. Evidence from ONWARDS 6 and our modeling support that the higher hypoglycemia risk is manageable and can be mitigated, consistent with daily basal

insulin products. Episodes of hypoglycemia occurring with insulin icodec are no different than those occurring with daily basal insulins. The duration and management of these events will be the same with insulin icodec as with daily basal insulins.

Importantly, evidence from ONWARDS 6 identified no unique characteristics that place any subgroup at differential relative hypoglycemia risk versus insulin degludec. Since hypoglycemia is the most common risk with any insulin, physicians are already familiar with risk factors and mitigation strategies to avoid it. We will reinforce these measures for healthcare professionals and patients who use weekly insulin icodec.

Based on our extensive investigations and analyses, we have proposed strategies to lessen the risk of hypoglycemia and enhance the benefit-risk of insulin icodec in people with type 1 diabetes. The first step occurs with the selection of individuals, identifying those who could benefit from less frequent dosing. An important aspect of

selection will be avoiding those with inherently high risk of severe hypoglycemia like those with hypoglycemic unawareness or people who experience recurrent severe hypoglycemia. For example, the available materials and label will make clinicians and patients aware that hypoglycemia risk could be increased on days 2 to 4 of the dosing cycle, recognizing that some, but not all people, could be affected.

We also recommend CGM use for people with type 1 diabetes treated with icodec since this will be the best aid as a guide for needed dose adjustments. Healthcare professionals are well acquainted with managing hypoglycemia, and these measures align with today's individualization of antihypoglycemic therapy such that dosing will be adapted to the needs of each person. We look forward to working with the FDA to align on product labeling and tools to enhance the patient's experience based on today's discussion and your insights.

Finally, insulin icodec represents a

valuable option for people with type 1 diabetes who use a basal bolus regimen to manage their diabetes and who want to reduce the burden of daily administration. Our presentation demonstrates that this can be accomplished with a favorable benefit-risk. Thank you. We'll be happy to address your questions.

Clarifying Questions to Applicant

DR. LOW WANG: Thank you so much for these presentations.

We will now proceed to clarifying questions for Novo Nordisk. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your

follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I would like to take the chair's prerogative and start with the first question. First of all, this was really great information, so I appreciate that. I was surprised there were no characteristics that identified those who are at higher risk for hypoglycemia that possibly increased glycemic variability. Of course, clinical trial settings are not necessarily similar to real-world settings, and they might underestimate the rate of hypoglycemia, so I was wondering about exclusion criteria.

Were patients with hypoglycemia unawareness or recurrent hypoglycemia excluded from the trial for type 1 diabetes?

DR. GOUGH: Yes, that is correct. In type 1 diabetes, we had a fairly broad inclusion criteria, but those two characteristics that you describe in terms of hypoglycemic awareness and severe recurrent hypoglycemia, they were an exclusion

criteria for ONWARDS 6, as is standard in these trials at this stage.

DR. LOW WANG: Alright. Thank you.

So let's take questions from our panel. First, Dr. Kalyani.

DR. KALYANI: Thank you for those really insightful presentations. I had a few clarifying --

DR. LOW WANG: I'm sorry. Can you please state your name?

DR. KALYANI: Yes. Hi. Rita Kalyani. I had a few clarifying questions. The first is to follow up on the question from Dr. Low Wang about subgroups. You presented a really nice slide about subgroups; however, I wondered if you also stratified the frequency of hypoglycemia by baseline A1c. Given the profile that we see for our weekly insulin icodec, you might expect that perhaps those with a higher baseline A1c within that 7 to 10 percent eligibility would have a lower frequency, and I was curious if that was an a priori stratification on what you found.

DR. GOUGH: What I can tell you is that we have looked at a number of baseline characteristics and a number of clinical characteristics within our patients, and the the risk factors that we identified for hypoglycemia are those risk factors that are well reported in the literature. So, for example, this included, in addition to high glycemic variability, a longer duration of diabetes and a lower body mass index.

We did not specifically find a relationship to the baseline A1c that you described, and certainly not a significant clinical relationship to baseline A1c, but the risk factors we did identify are those risk factors that you see in the literature; and the other important point is they were comparable between both insulin icodec and insulin degludec.

DR. KALYANI: Thank you. I had one other question as well. As mentioned very nicely in the background, we would expect that a weekly injection could potentially improve medication taking behavior and reduce treatment burden. However, in

the diabetes questionnaire that was given to participants in ONWARDS 6, it was actually not found as hypothesized; in fact, some of the questions such as would you recommend this to someone else with diabetes compared to insulin degludec and how flexible have you been finding your treatments, icodec versus degludec were unfavorable for the icodec arm. And while these were aggregate data and don't represent individual preferences, I wonder if you could comment a little bit more on why that might have been.

DR. GOUGH: Yes. So you're correct that in ONWARDS 6, we conducted the Diabetes Treatment Satisfaction Questionnaire, which is a PRO looking at treatment satisfaction. I think it's important to point out that there are, as you know, significant limitations of conducting PROs within a randomized-controlled trial.

If we look at what would be considered a clinically relevant improvement in the score based on the literature of 0.5 standard deviation improvement from baseline, we saw an improvement in

the total score of 45 percent for insulin icodec and 48 percent for insulin degludec, but as you say, there are many limitations in conducting patient-reported outcomes studies in an RCT such as ONWARDS 6. But maybe I could call upon my clinical expert to comment a little bit further on where she would see the value of this once-weekly insulin in terms of patient satisfaction, so I'll call upon Dr. Lingvay.

DR. LINGVAY: Thank you. Ilda Lingvay. I think there are a few points that we need to be aware of. The first one is, in these studies, patients that get enrolled are not the ones that necessarily might benefit the most from insulin icodec, so that needs to be kept in mind. The second point that's very important, both groups improved their treatment satisfaction while in the study. In fact, it's interesting that that happened because half of the people at baseline that were randomized with degludec, they actually were on degludec prior to the study, so it's interesting that they improved their treatment

satisfaction so much even though they didn't really change their treatment. So I think that illustrates how difficult it is in a clinical trial to actually pick up on these differences in quality-of-life or treatment satisfaction.

DR. KALYANI: Thank you.

DR. GOUGH: Thank you.

DR. KALYANI: I do have some other questions, but I'll let others ask theirs, and then ask mine at the end. Thank you very much.

DR. LOW WANG: Perfect. Thank you.

Next, I'd like to call on Dr. Brittain.

DR. BRITTAIN: Hi. It was a very nice presentation. Thank you. I want to bring up slide CO-55. Obviously, there's a very big difference across the the dosing week, and I'm asking a question from a little bit of a different angle, not the hypoglycemia angle. But day 6 and 7, or maybe day 1, I wonder if there's potential for more high glucose readings those days and if that's something that you looked at, if you looked at time in range, time above range, time below

range as a function of each of the dosing days.

DR. GOUGH: Yes, we did do that, yes, and clearly, that's an important consideration. What I can share with you are the continuous glucose monitoring the time within range, the time above range, and time below range on each of the days of the week.

So what I'm showing you here is, first of all, CGM ranges -- let me just orientate you -- is the same as the core presentation, but the green is time within range, the yellow and orange are time above range, and then the gray and red, time below range. On the Y-axis, we see percentage time in range, and then on the X-axis, we're looking at the day of the dosing cycle, so day 1 is the day in which insulin icodec is administered. And what you can see here is that over the period, there is more time in range on days 2, 3, and 4, but importantly, even days 6 and 7 -- over 58 percent on day 6 and 56 percent on day 7 -- also showed time in range, and importantly no increase in time below range.

So there are some differences over the week,

but I think what's also important is then when we look at A1c, we have noninferiority compared to a once-daily insulin, showing that once-weekly insulin icodec is effective in terms of delivering glycemic control across the week, including within its pharmacodynamic profile.

DR. BRITTAIN: Okay. Thank you.

DR. LOW WANG: Next, Onumah.

DR. ONUMAH: Hi. Barbara Onumah. Thank you for the presentation. I just have two follow-up questions. One is specifically for the question about the FDA requirements or requests to do a third arm in the type 1 study that should include the 2 times per week dose. We didn't get any information on that, and I was wondering if that was done.

DR. GOUGH: Yes. First of all, I'd very much like to say that we very much appreciate the constructive dialogue that we had with the agency around the development of the phase 3 program and the use of a twice-weekly insulin icodec. We opted to go for once-weekly insulin icodec based on the

terminal half life, which is over 170 hours, and our earlier data supported that we would be able to administer insulin icodec once weekly.

The aim of developing insulin icodec was to have, and is to have, a once-weekly insulin. If it was to be administered twice weekly, I think that would add to the complexity of diabetes treatment in patients with type 1 diabetes. So, for example, which day of the week would it be taken if it was to be split into a twice-weekly injection? Would it be 3 days apart? Would it be 4 days apart?

So the clinical utility of twice-daily insulin icodec I think would be questionable, but when you look at the data that we generated in ONWARDS 6, we've demonstrated noninferiority, we've demonstrated similar time in range, we've demonstrated similar time below range in keeping with international guidelines, and with a very low rate of level 3 hypoglycemia with 3 percent in each treatment arm, no difference in terms of the proportion of patients with a similar safety profile. And when hypoglycemia does occur -- and

we acknowledge that hypoglycemia does occur -- it can be managed in exactly the same way as a once-daily insulin.

So we very much appreciated the dialogue with the FDA, but ultimately our ambition was to develop a once-weekly insulin, which we believe we've demonstrated with ONWARDS 6.

DR. ONUMAH: Thank you. One quick follow-up question was about the modeling. I think it was great that there were a few models that were presented that could guide clinicians in how they could do adjustments in prescribing this insulin for all persons with diabetes, including persons with type 1 diabetes. I was wondering if there was any modeling considered for inpatient or persons who are hospitalized, or if there was any information noted for hypoglycemic episodes that happened during those times, because as one could imagine, when people are in an acute setting for illness, their insulin needs and requirements change, and hyperglycemia, as well as hypoglycemia, could occur.

DR. GOUGH: Yes. Thank you very much for that question. Within the ONWARDS program, including in ONWARDS 6, we did have patients, as you would expect, who were hospitalized for both medical and surgical reasons. And when we look at the rates of hypoglycemia and the management of glycemia while patients were in hospital, it was no different between those that were admitted on a once daily versus those with a once weekly.

So our data support that the management of patients who are hospitalized on once-weekly insulin can be exactly the same as that for a once daily. And what I would point out is I can tell you that in our ONWARDS 6 trial, in patients with type 1 diabetes, there were no level 3 hypoglycemic episodes during hospitalization for either insulin icodec or indeed daily basal insulin.

DR. ONUMAH: Thank you.

DR. LOW WANG: Thank you.

MR. TIBBITS: Thank you, and thank you for the presentation. Dr. Onumah, thank you for asking one of my questions about the twice-per-week

treatment regime.

My other question is you referenced approval by other regulatory authorities, Switzerland, Canada and EMA, I believe. Can you talk about any labeling restrictions or other risk mitigation strategies that those regulatory authorities may have asked in the type 1 setting?

DR. GOUGH: Certainly. As you point out, there are three areas where insulin icodec has already been approved for use in patients with type 1 and type 2 diabetes, and to give you some insights from those other regulatory authorities, I will call upon Shawn Hoskin, our Executive Director in Regulatory Affairs here in the U.S.

MR. HOSKIN: Shawn Hoskin. The indications for the products that were approved for icodec, that was approved in Canada, EU, and Switzerland, is a complete indication, so it's for once-weekly treatment of adults with diabetes mellitus to improve glycemic control for both type 1 and type 2 diabetes. There is information in all the labels which describe that the maximum glucose lowering

effect occurs during days 2 to 4, and that is important information because there's a potential increased risk of hypoglycemia on those days. There are also risk mitigations that icodec should not be used in patients with a history of hypoglycemia unawareness, and that if a patient does experience recurrent hypoglycemia, they should consult their healthcare provider to consider treatment adjustments or alternative treatment options.

Within the EU label, I think it's relevant that there's a risk mitigation that patients with type 1 diabetes should only be treated with insulin icodec if there's a clear benefit from a once-weekly pathology expected. I think those are the highlights of the relevant risk mitigation from the three different areas where icodec has already been approved.

MS. TIBBITS: Great. Thank you very much.

DR. LOW WANG: Okay. Terrific. Thanks.

Next, Dr. Nason.

DR. NASON: Thank you. Martha Nason from

NIH. My question is about the subgroups using CV. In these analyses, the CV was measured after the baseline, so it was measured on the first 2 weeks, I believe, of treatment with either icodec or the daily comparator, which obviously are different, so that may not select the same patients as below 36 when some of them are responding to the icodec and some of them to the daily.

So I was wondering if you'd been able to measure CV at baseline and could do the same subgroup analysis using their baseline CV. And as a tangential question in trying to think whether the CV would be useful clinically moving forward, how available -- this is the question I guess for the clinicians -- and reliable is CV in a clinical setting if a patient is coming in and interested in this treatment? How much would you have that information and how reliable would it be?

DR. GOUGH: There are a number of components to that question or a number of ways that I would like to answer it. The first is that we have looked at the glycemic variability throughout the

whole duration of the trial, over 52 weeks, and I think you've seen these data in the FDA briefing book, and what you can see is the consistency over the full period, so over 52 weeks, both insulin icodec and insulin degludec, there's consistency in terms of that glycemic variability even though we didn't have it pre-randomization, and I think that's extremely reassuring that the glycemic variability isn't changing. We can also show you that we can assess glycemic variability based on either CGM or SMBG values, and there's a very strong correlation between those.

In terms of do we have any data pretreatment, maybe what I can do is call upon my senior medical director, Roman Cailleteau, who can tell you something very briefly about our phase 1 trial where we did have some of these data.

DR. CAILLETEAU: Roman Cailleteau. Just to confirm, in our ONWARDS 6 trials in phase 3A, we did not have baseline CV, so we cannot reproduce the different analysis that we showed you during the presentation or one I think in the FDA briefing

book with baseline CV. However, we have looked into -- and that has been said already -- how stable is the glycemic variability over time and what we had in our trial, could it be predicting, for example, if we selected patients at baseline, so before introducing insulin icodec.

We had a clinical pharmacology trial where we treated patients with insulin icodec, and it was a crossover design. So we have one of the arms, and you can see it's a highlight of this trial scheme where patients started 2 weeks on insulin glargine and then they switched to insulin icodec for an 8-week treatment.

We've looked, and we had CGM for both of these periods. So we've looked into the CV and if it was stable when switching from insulin glargine for this sequence that was a crossover to insulin icodec, and as you can see it's 2 weeks for insulin glargine and the first 14 days or the first 2weeks for insulin icodec. The mean CV is very stable, so 35.76, and it's stable then around 35.86, so very stable, and there was almost no patients switching

between the groups.

DR. NASON: So this doesn't actually say whether they were individually stable. But you're saying they were if you looked at, say, a scatter plot of their CV on the first one versus the second, that would also be very linear, I guess, very highly correlated.

DR. CAILLETEAU: Yes, we can confirm that.

DR. NASON: Great. Thank you.

DR. LOW WANG: Thank you.

Next, Dr. Kalyani.

DR. KALYANI: Thanks. Rita Kalyani. So my question has to do with the dose titration schedule that was done in ONWARDS 6. In the supplementary tables 2 and 3, it describes the weekly titration that was done for both basal and bolus insulin, and not surprisingly, insulin icodec had a higher proportion of basal to bolus insulin that was given compared to degludec, consistent with the findings that the efficacy was similar with a higher hypoglycemia.

So I found it interesting that it was

described that some participants on their own increased either bolus insulin during days 2 to 4 or they reduced it during days 2wo to 4, and I was curious how often dose titrations had to occur on a weekly basis in this clinical trial and how often one might expect that in a real-world setting, people with diabetes would be able to individually titrate their doses to accommodate what we know is the peak and the wearing off of active insulin icodec.

DR. GOUGH: Yes. So we did have patients within ONWARDS 6 who reduced their bolus dose. They reduced their bolus dose on days 2, 3, and 4. I think it's important for me to point out that they they only reduced their bolus dose in a reactive way by a very small order of magnitude. So our modeling would recommend that around a 30 percent dose reduction, which would equate to 1 to 2 units with each meal, would be helpful in terms of mitigating or reducing the risk of hypoglycemia.

In our clinical trial, we didn't see that.

We didn't see that magnitude of reduction, so we unfortunately wouldn't then have seen that contribution to reduction in terms of hypoglycemia. But as I say, the order of magnitude we're talking about is that what we would see in routine clinical practice. And maybe to comment a little bit further, you asked about the real-world setting. Again, maybe I could call upon my clinical expert, Dr. Lingvay, to give her perspective on that.

DR. LINGVAY: Thank you, and thank you for that question. It was interesting that you noted that in the study, patients and providers eventually did learn how to manage this insulin, and even though they weren't told up front how to manage the bolus, they caught on eventually. It's actually important to know that by the end of the extension phase, the time below range was actually exactly the same for both groups, which does point out the fact that patients and providers, we do learn how to use a new insulin and eventually figure out how to individualize treatment for each patient. I can actually show you that if I can

figure out how to do that.

There you go. So by the end of the treatment, this is time below range comparing the two groups, and then by the end of the extension phase in those weeks 48 through 52, there were exactly identical time below range, and the time below range improved over time in patients treated with icodec.

The other point that I want to make that's very important, this 30 percent reduction in bolus insulin, I think it's a good strategy to do proactively; however, it's probably not needed in everybody. In fact, it's probably a subset of people that need it, and when applied, I think we showed that that will have a really good chance of minimizing these hypoglycemic episodes on those days, but it's just one of many mitigation strategies that can be applied.

You know very well, in clinic, we individualize treatment for really every patient, and while for some this 30 percent reduction is well appropriate, for others we might do other

interventions. I can think of one example. For example, if our patients at a time eat more over the weekends, we get on the CGM those weekend profiles and they always have high sugars over the weekend. Well, it might be a good time to inject this insulin on Fridays, and then you cover the weekends. So it's just one of many such strategies. I think it's very good for the label to suggest this, for people to think about it, but it's not the only option, and it's probably not needed for everybody.

DR. KALYANI: Thank you.

DR. LOW WANG: Next, I'd like to call on Dr. Beringer.

DR. BERINGER: Hello. Paul Beringer. My question relates to the modeling that was done. The PK/PD model accurately predicted the week 26 fasting glucose and the GMI data from the ONWARDS 6 trial showing that it does a good job of predicting the outcomes, and that was successfully applied to determine the reduction in the bolus insulin that would help mitigate some of the hypoglycemia.

My question relates to whether this model was applied and looking at alternative regimens, namely the twice-weekly injections. You already addressed the desire to have once weekly, but I'm just wondering whether the modeling was applied to look at that because if you could flatten things out, the pharmacodynamic effect, then you may not have to restrict use through these risk mitigation strategies. Thank you.

DR. GOUGH: Yes. So we did look at a range of scenarios in terms of what changes could we make. In terms of the basal insulin titration scenario, we looked at if you monitored your blood glucose on different days of the week. So if you use, for example, days 2, 3, and 4 or used the whole week, would that have an impact in terms of your dose adjustment and glycemic control, and the risk of hypoglycemia?

We looked at whether making dose adjustments every fourth week rather than weekly would have an impact, and also using titration increments of 10 units rather than 20 units. We also considered

looking at a higher glycemic target within the first 8 weeks, but ultimately, having looked at all of these different scenarios, we identified that actually the bolus dose reduction, the potential bolus dose reduction, of an order of magnitude of around 30 percent on days 2, 3, and 4 was the most effective way of reducing hypoglycemia, or the risk of hypoglycemia, whilst at the same time preserving glycemic control.

For reasons I gave early, we did not look specifically at a twice-weekly injection. Our ambition has been to reduce the burden and the complexity of disease by administering a once-weekly insulin, but we have looked at different scenarios, as I say, and the best is to consider a change to the bolus on days 2, 3, and 4.

DR. BERINGER: Thank you.

DR. LOW WANG: Alright. Thanks.

Next, Dr. Greevy.

DR. GREEVY: Hi. This is Robert Greevy. My one question is, can you discuss the protocol for somebody who misses their dose of insulin icodec on

their normal day. Say I normally take it on Sundays, and then I wake up Monday and realize I hadn't taken it, what is the protocol?

DR. GOUGH: If this is approved and the patient misses their insulin icodec dose, we would advise them to take it as soon as they remember. And that's what happened within the trial, with a slight difference within trial, but I can come back to that. But essentially, we would advise them to take the next dose as soon as they remember and do the usual things that you would do with type 1 diabetes in terms of regular blood glucose monitoring.

Then in terms of the follow-up dose after remembering, the important point then is to have a 4-day gap between the next injection. Now clearly, what that might do is then move your injection from your favorite day, but we then know that because you have that flexibility of 3 to 4 days, you can then move it back again in time. So the advice is take it straight away as soon as you remember and not have 2 doses closer than 4 days together. So

there's a lot of flexibility with this once-weekly administration.

DR. GREEVY: Very good. Thank you.

DR. LOW WANG: Thanks for asking that question. That was actually going to be my question about missed doses and early doses.

So next I'd like to go to Dr. Nason.

DR. NASON: Thank you. I actually wanted to go back to my question because I realized that I had asked a two-part question about the CV values, and you all had answered the first, and I'd been satisfied; and then as soon as I turned off my camera, I realized that there had been a second part, which was, how well is the CV measured and available clinically for patients who might come into the clinic and be interested in this? I don't have a sense as a statistician of how available that data would be on potential users.

DR. GOUGH: Currently, around 30 percent of patients on multiple daily injections use CGM as a method of assessing their glycemic control. And as I mentioned, whether you use CGM or self-monitored

blood glucose profiling, the two methods are actually complementary. Maybe I can show you some data here where we looked at the relationship between self-monitored glycemic variability -- or glycemic variability from self-monitored glucose profiling -- compared to CGM, and you can see there's a very strong correlation between whether you measure it by CGM or SMBG. But to give you a more clinical perspective, maybe I can call upon my clinical expert, Dr. Lingvay, as to how she sees this.

DR. LINGVAY: Thank you. Ilda Lingvay. The CV is one of the standard readouts that we get from patients, from every patient that comes into the clinic. So they hand over their CGM or their blood sugar meter to the nursing staff, they plug it in the computer, and we get a list of variables. This is standard for patients with type 1 and type 2 diabetes, but especially for patients with type 1. We do this for every single patient that steps into the clinic.

We get their report on time in range, time

below range, time above range, coefficient of variation, mean glucose. There are a number of variables that we use clinically pretty much on a regular basis for every clinic visit. And I think it's important to point out that for those people who are using CGM, we have them, but also for people who are using finger sticks, we also get the same report from the downloaded machine.

DR. NASON: Thank you.

DR. LOW WANG: Just a quick comment. I actually haven't seen CV for our patients. With SMBG, we might get a standard deviation. Anyway, to go on to the next question, Dr. Brittain.

DR. BRITTAIN: Yes. Erica Brittain. A few questions ago, we saw a slide that showed time in range getting closer between the arms over time. And I don't know the number of that slide, but I was wondering is there any possibility there could be some dropout going on, especially in the very later weeks that are past the primary endpoint so that people who are having a lot of hypoglycemia are dropping out. I'm just wondering about the

potential for bias in that slide, if someone could bring it up. I don't know the number.

DR. GOUGH: Yes. First of all, you're quite right. There are significant limitations with looking at the data over a 12-month period and there are many variables that may come into account. What I can say is that the completer rates at the end of the extension phase was also high, and there was no preferential fallout, or in terms of patients leaving the trial in terms of hypoglycemia, the rates were extremely low.

As we mentioned in the presentation, completer rate during the main part of the trial was also extremely high, over 90 percent, and we saw similar consistency during the extension period, but you raise an important point.

DR. BRITTAIN: Okay. Thank you.

DR. LOW WANG: Thank you.

Next, Dr. Beringer?

DR. BERINGER: No, my question was addressed already. Thank you.

DR. LOW WANG: Okay. Terrific.

Then going on to Dr. Dutta.

DR. DUTTA: Thank you, Sandeep Dutta. My question is a follow-up to Dr. Brittain's first question, on slide 55, where you show the hypoglycemia over time during the week. My question is specifically about the risk mitigation in the morning that was done, such as reduction in 30 percent in the bolus injections. I was wondering if you have a display of what that mitigation will result in, specifically in reduction in hypoglycemia on days 2 through 4.

DR. GOUGH: Our anticipation from the model was that by applying the 30 percent dose reduction, we could see somewhere in the order of magnitude of a 50 percent reduction in terms of hypoglycemia, but specifically to show you the impact of that dose reduction from the model, I will call upon my senior medical director, Roman Cailleteau, to share some data with you.

DR. CAILLETEAU: Roman Cailleteau. The data that we presented during the core presentation, we can see there's a modeling result. When we reduce

by 30 percent bolus insulin doses on days 2 to 4, we are able to maintain a change in A1c that is very close to the model data of ONWARDS 6 to a minus 37 percent -- open 37 percent -- by reducing around half the hypoglycemia rate from 21 to 12.8.

But specifically, I think your question was about did we look into the rates on days 2 to 4 specifically, if they were also reduced. We didn't look specifically in these, but from this data, you can see a 50 percent reduction applies. Probably most of these episodes are reduced on this time of the week, so days 2 to 4.

DR. DUTTA: Thank you.

DR. LOW WANG: Okay. Thank you.

If there are no more questions -- oh, actually there is one more question, so Dr. Onumah, please.

DR. ONUMAH: Hi. It's a quick question about labeling.

DR. LOW WANG: I'm sorry. Could you please state your name? Thank you.

DR. ONUMAH: Sorry. Barbara Onumah, and a

question about labeling for this insulin in other places and other countries where it has already been approved. I think it was asked before, I guess restrictions or recommendations that have been put in the package insert for clinicians. And I noticed in the study, the inclusion criteria was specifically for persons with type 1 diabetes who have been diagnosed over a year. So I wonder if that's also clearly stated in there because, as one could imagine, when people are newly diagnosed with type 1 diabetes, there are lots of fluctuations and changes, and that could be a potential concern when using such a long-lasting basal insulin.

DR. GOUGH: Yes, that's an important point. The patients that were recruited into our study were patients who'd had type 1 diabetes for 12 months, and we would envision, although necessarily a specific restriction, patients considering a once-weekly insulin injection, a basal insulin injection, would be patients maybe familiar with the management of type 1 diabetes, how they monitor their blood glucose profiles, and

how they adjust two different insulins.

So I think that's a really important question, but at the same time, we didn't specifically look at patients who had type 1 diabetes for a shorter period of time.

DR. ONUMAH: Just to follow up, my question specifically was, was that stated anywhere for clinicians, who may be using this as a caution for them, to be able to not use it in persons who have not had type 1 diabetes for that long or who have not been diagnosed for that long.

DR. GOUGH: Yes. I think that's a question that we would look forward to discussing with the agency.

DR. ONUMAH: Thank you.

DR. LOW WANG: Thank you, and then Dr. Kalyani.

DR. KALYANI: Thanks. Rita Kalyani. On table 10-8 in sponsor's briefing document, I found it interesting that while it's been commented on that the duration of hypoglycemia episodes between icodec and degludec were similar, that the

frequency was actually a little different between the two arms, in that those who were on icodec were more likely to have recurrent hypoglycemia episodes compared to those in degludec. For instance, 1 to 9 episodes was 139 in icodec versus 171 in degludec, but 10 to 19 episodes was 65 in icodec versus 35 in degludec, and more than 20 was 43 in icodec versus 17 in degludec.

I appreciate the comment that there was a participant who had more than 30 episodes, but it does seem that there is a trend to more recurrent episodes in those who have it. And I was curious to know if this was hypoglycemia that took longer to treat -- for instance, you treat it, it's still low, you treat it again -- or were these recurrent hypoglycemic episodes that occurred on different days.

DR. GOUGH: So there are a number of components to your question there. First of all, I would just highlight that the duration of hypoglycemia with insulin icodec in our ONWARDS 6 trial was exactly the same in terms of the duration

of the episode; the once weekly was the same as the once daily. I can also point out that if we look at CGM after an episode of hypoglycemia and we looked at time below range for a number of days after an episode of hypoglycemia, the amount of time below range after an episode of hypoglycemia was similar for a once daily as a once weekly.

I'd also point out that the management of hypoglycemia was exactly the same in both treatment arms. In terms of the protocol, we didn't suggest anything differently for patients on insulin icodec. We gave exactly the same advice in terms of how hypoglycemia should be managed. And again, when we showed you the management of level 3 hypoglycemia in the ONWARDS 6 trial, we showed you there was, again, no difference between once weekly and once daily. And actually, in terms of level 3, over 8 percent of patients in both treatment arms were managed similarly with oral glucose intake.

So I think to sort of pull all of that together, the duration of hypoglycemia is similar, the management of hypoglycemia is similar, time

below range after a hypoglycemic episode is similar, and our data show that the increased risk of hypoglycemia and when hypoglycemia does occur, it can be managed in exactly the same way.

DR. LOW WANG: Alright. Thank you.

Now, let's take a 10 minute break until 11:12 Eastern Time. We'll resume at 11:12 Eastern Time. Thank you all.

(Whereupon, at 11:02 a.m., a recess was taken, and meeting resumed at 11:12 a.m.)

DR. LOW WANG: Welcome back.

Just a quick comment before we continue, Dr. Kalyani and panel members, we may have more time for clarifying questions after the open public hearing in case there are more points needing clarification.

So we will now proceed with FDA's presentation, starting with Dr. Leslie Kenna.

FDA Presentation - Leslie Kenna

DR. KENNA: Good morning. My name is Leslie Kenna, and I'm the Clinical Pharmacology Reviewer of the insulin icodec application. Over the next

four slides, I will discuss exposure and pharmacodynamic response to insulin icodec and how the dose of insulin icodec was selected for patients with type 1 diabetes.

The applicant conducted two phase 1 studies of the pharmacokinetics and glucose lowering pharmacodynamic of insulin icodec in patients with type 1 diabetes. In these studies, patients were administered insulin icodec by subcutaneous injection once weekly for 8 weeks at a dose that was unit matched to their daily basal insulin dose established during a run-in period.

This figure shows insulin icodec concentration over time in 65 patients in one such study. Drug concentration is plotted for 168 hours post-dose, which is 1 week, because this is the proposed dosing interval. Note that, on average, maximum drug concentration is reached on the first day of dosing at about 18 hours post-dose, then drug concentration goes down over the week until the next dose is administered. The elimination half-life of insulin icodec averages about 1 week.

Now, let's consider data on the pharmacodynamic response to insulin icodec. This histogram shows the glucose lowering response to insulin icodec in patients with type 1 diabetes as measured in a euglycemic clamp study at steady state. Patients received an infusion of glucose to keep their glycemic level within a target range. A higher glucose infusion rate, or GIR, means that patient glucose levels were below target and a higher level of glucose needed to be infused to stay at the target glycemic level.

Here on the Y-axis, you see the percent of area under the GIR curve. If patients receiving insulin icodec achieved an even glycemic level throughout the week, we'd expect these bars to be the same height every day. Because this is a histogram, the percents over the week should add up to 100, so in the ideal case, 100 over 7 would be a little over 14 percent per day. As you can see, the peak GIR effect occurs on days 2 to 4 post-dose and declines until the next dose. This reflects that more glucose needed to be infused on day 2

compared to day 7 to keep glucose levels in the target range.

The insulin action profile for insulin icodec is different than for the approved daily basal insulin. Here's what the insulin action profile looks like in patients with type 1 diabetes according to the label for two approved daily basal insulin products. First, consider insulin degludec in the figure on the left. The shaded area shows the glucose infusion rate in a euglycemic clamp study for the 24-hour period after dosing at steady state. Next, consider insulin glargine in the figure on the right. The solid line shows the glucose infusion rate after a single insulin glargine dose was administered. Because these products are administered daily, the same pattern repeats every day of dosing.

I'd like to walk you through the rationale for the proposed insulin icodec dosing regimen for patients with type 1 diabetes. A once-weekly regimen was based on the week-long half-life of insulin icodec. The amount administered was

determined by unit-to-unit matching of a patient's existing daily basal insulin dose multiplied by 7 to scale up from a daily dose to a weekly dose. This assumes that the patient's current daily basal insulin intake and insulin icodec have an equimolar ratio. A loading dose was used to reduce time to steady state from 2 to 4 weeks to 2 to 3 weeks.

Dr. Frank Pucino will now review the study design features of ONWARDS 6, the clinical trial used to support the type 1 diabetes indication.

FDA Presentation - Frank Pucino

DR. PUCINO: Good morning. My name is Frank Pucino. I'm the clinical reviewer for this application. On the next several slides, I will briefly discuss the study design features of ONWARDS 6, the applicant's only phase 3 trial conducted in patients with type 1 diabetes.

The applicant's phase 3 development program included six adequate and well-controlled trials, ONWARDS 1 through ONWARDS 6. ONWARDS 1 through 5 included type 2 diabetes patient populations, while ONWARDS 6 enrolled patients with type 1 diabetes.

In these trials, subjects were randomized to insulin icodec or comparators, which included insulin glargine, insulin degludec, or other basal insulins. A 1 to 1 treatment allocation was used for all trials. Both ONWARDS 4 and 6 included multiple daily insulin injections with insulin aspart used as the bolus insulin for all subjects. This presentation will primarily focus on ONWARDS 6.

ONWARDS 6 was a 1 to 1, randomized, open-label, active-controlled, parallel group, treat-to-target phase 3 trial. In this trial, the efficacy and safety of insulin icodec in adult subjects with type 1 diabetes was compared to insulin degludec both in combination with insulin aspart. The trial duration was 59 weeks and included a 2-week screening period, a 26-week main treatment period, a 26-week extension phase, and a 5-week follow-up period. At week 52, subjects were transferred to a marketed basal insulin product at the discretion of the investigator.

Adult patients with type 1 diabetes who were

treated with multiple daily insulin injections for at least one year and had an A1c less than 10 percent at screening were excluded if they met any of the exclusion criteria included in this slide. Of note, subjects with severe renal impairment, hypoglycemia unawareness, and recurrent hypoglycemia, which are all considered important risk factors for hypoglycemia, were excluded from study participation.

The patient population randomized into ONWARDS 6 was generally young and white. Participants also had relatively good glycemic control with a mean baseline A1c of 7.6 percent and normal renal function with a mean eGFR of 98 mLs per minute. To mitigate the risk of hypoglycemia during the first week of treatment, subjects randomized to the insulin icodec arm received a loading dose. The initial insulin icodec dose administered was equivalent to the total daily basal dose before randomization multiplied by 7. A one-time additional dose also was administered depending on the A1c level prior to randomization.

If the A1c was less than 8 percent at screening, a one-time 50 percent loading dose was applied. If the A1c was greater than or equal to 8 percent, a single 100 percent loading dose was applied.

Subjects switching from insulin glargine U-300 or basal insulin twice daily received a 50 percent loading dose of insulin icodec regardless of their A1c at screening. Subjects randomized to the insulin degludec arm were switched from their pretrial basal insulin according to local labeling. The bolus dose was switched to insulin aspart on a unit-to-unit per meal basis.

The recommended dose titrations for insulin icodec, insulin degludec, and insulin aspart are shown on this slide. The basal dose adjustment shown on the top portion of this slide was based on the lowest of three pre-breakfast, self-measured, plasma glucose values, referred to as SMPG, which were measures on 2 days before and on the day of each weekly dose titration. The insulin aspart dose adjustments, done weekly using either the

prespecified algorithm shown on the bottom portion of this slide, were based on carbohydrate counting at the investigator's discretion.

During the first 8 weeks, adjustments in bolus doses were to be made only for safety reasons. Weekly dose adjustments were based on the lowest preprandial or bedtime SMPG values measured the week prior to titration. The breakfast dose was adjusted based on the pre-lunch SMPG value, the lunch dose was adjusted based on the pre-dinner SMPG value, and the dinner dose was adjusted based on the bedtime SMPG value.

Subjects used a Dexcom G6 CGM device for the entire duration of the trial. Alerts for low or high glucose values were not blinded to either subjects or investigators. Subjects also received a glucose meter and were instructed to measure a 4-point daily SMPG at pre-breakfast, pre-lunch, pre-dinner, and bedtime throughout the trial. The measured SMPG values were subsequently transferred daily into an electronic diary by the subject.

I will now turn the presentation over to

Dr. Roberto Crackel from the Division of Biometrics II, who evaluated the efficacy of insulin icodec for the ONWARDS program.

FDA Presentation - Roberto Crackel

DR. CRACKEL: Thank you, Frank.

Good morning. I'm Dr. Roberto Crackel, a Senior Mathematical Statistician at FDA. I'm the primary statistical reviewer for efficacy. I will be providing the efficacy findings from the ONWARDS 6 clinical trial.

ONWARDS 6 was a randomized, open-label, active-controlled trial. Participants were randomized 1 to 1 to either insulin icodec or insulin degludec. There were two phases. The main phase was the first 26 weeks at which the primary endpoint was measured for efficacy, followed by the extension phase for an additional 26 weeks for safety with a 5-week follow-up period.

The primary objective was to confirm the effect on glycemic control of once-weekly insulin icodec in participants with type 1 diabetes by comparing the difference in change from baseline in

A1c between once-weekly insulin icodec and once-daily insulin degludec, both in combination with insulin aspart after 26 weeks of treatment to a noninferiority margin of 0.3 percent.

The primary estimand was the treatment policy estimand which consists of the following five components. The treatment condition was insulin icodec or insulin degludec irrespective of adherence to randomized treatment and changes to anti-diabetic background medication. The primary endpoint was change from baseline to week 26 in A1c.

The population was adults with type 1 diabetes and at least one year of treatment with multiple daily insulin injections on a basal and bolus insulin analog regimen. Intercurrent events were treatment discontinuation or withdrawal from the trial. All available data, regardless of treatment discontinuation, was used in the analysis. The population level summary measure was the difference in mean changes from baseline in A1C at week 26 between insulin icodec and insulin

degludec.

For handling the missing data, the applicant's prespecified approach was to multiply impute missing data regardless of treatment completion status, based on observed data from participants who discontinued treatment but remained in the study and had their final week 26 endpoint measurement. The results of this analysis were reported in the submission and were independently replicated by FDA.

Of note, for the statistical analysis plan, if the number of participants who were off treatment with week 26 data is insufficient for meaningful imputation, a return to baseline approach would be taken whereby the participants' endpoint measurement is drawn from a normal distribution centered at the participants' baseline measurement with a random error.

This table summarizes the data capture disposition for A1c measurements at week 26. The full analysis set was defined as all randomized participants. There were 290 participants

randomized to insulin icodec and 292 randomized to insulin degludec. On insulin icodec, there were 274 participants with observed A1c measurements, five of whom were off treatment, and there were 16 participants with missing A1c measurements. On insulin degludec, there were 283 participants with observed A1c measurements, two of whom were off treatment, and there were 9 participants with missing A1c measurements.

Thus, for the prespecified approach for handling missing data, on insulin icodec, 5 participants were used to represent the 16 participants with missing data, and on insulin degludec, 2 participants were used to represent the 9 participants with missing data. Since the number of participants who were off treatment with week 26 data is small relative to the number of participants with missing data, FDA performed multiple imputation using the return to baseline approach. This presentation includes the results using the return to baseline approach.

Participants with missing week 26 data had

their missing measurement imputed 1,000 times and thus generated 1,000 complete data sets. For each complete data set, an ANCOVA model with the following fixed effects were used: treatment, region, pretrial basal insulin use, and screening A1c group. As a covariate, continuous baseline A1c measurement was used. Rubin's rule was used to synthesize analysis results from the 1,000 multiply imputed data sets.

Here are the results for the primary endpoint. The least squares mean reduction from baseline for insulin icodec is negative 0.47 and negative 0.52 for insulin degludec. The treatment difference is 0.06, and the lower bound of the 95 percent confidence interval is negative 0.05 and upper bound is 0.16. Therefore, noninferiority of insulin icodec is demonstrated since the upper bound of the 95 percent confidence interval is less than the noninferiority margin of 0.3 percent.

A two-way tipping point analysis was performed as a sensitivity analysis to confirm the robustness of the primary results by checking the

departures to the assumptions in the handling of missing data. The results were fairly robust because scenarios to tip the results from noninferior to inferior were unlikely, although not clinically impossible. Subgroup analysis results in age, sex, race, ethnicity, and region all support the consistency of the primary results with the overall population.

Secondary efficacy endpoints include the following: change from baseline to week 52 in A1c; change from baseline to week 26 and week 52 in fasting plasma glucose; time in range between 70 and 180 milligrams per deciliter during week 22 through 26 and week 48 through 52; and change from baseline to week 26 and week 52 in Diabetes Treatment Satisfaction Questionnaire Status Treatment Satisfaction scores, hereafter, DTSQ Treatment Satisfaction subscore. Items are summed from the DTSQ Treatment Satisfaction domain to generate a total treatment satisfaction score that ranges from 0 to 36, where higher scores indicate greater satisfaction with treatments. Of note,

secondary endpoints were not adjusted for multiplicity to control type 1 error for the study.

Analysis methods for secondary endpoints, the targeted estimand was the treatment policy estimand. The return to baseline approach for handling missing data was used for A1c, FPG, and DTSQ Treatment Satisfaction sub score; however, for time in range, no pre-baseline data were collected in the study. Therefore, missing data were imputed from a normal distribution centered at the average time in range for participants on insulin degludec who completed treatment with a random error. One thousand data sets were generated, ANCOVA was used for A1c, FPG, and DTSQ Treatment Satisfaction subscore and ANOVA was used for time in range to analyze each data set, and Rubin's rule was used to synthesize results.

Here are the results for change from baseline to week 52 in A1c. Both groups had reductions from baseline in A1c at week 52, with insulin degludec having a larger reduction. The treatment difference is 0.14, the lower bound of

the 95 percent confidence interval is 0.02, and the upper bound is 0.25, so the estimated treatment difference nominally favors insulin degludec.

Here are the results for the secondary efficacy endpoints of FPG, time in range, and DTSQ Treatment Satisfaction subscore at week 26 and week 52. For FPG at week 26 and week 52, both insulin icodec and insulin degludec had reductions from baseline; however, insulin degludec had more of a reduction as shown by the treatment differences. These differences nominally favor insulin degludec, as the 95 percent confidence intervals exclude zero; however, we note that FPG samples were taken before administration of either insulin icodec or insulin degludec in addition to insulin aspart.

For DTSQ Treatment Satisfaction subscore at week 26 and week 52, both insulin icodec and insulin degludec increased scores from baseline; however, insulin degludec had more of an increase, as shown by the treatment differences. These differences nominally favor insulin degludec, as

the 95 percent confidence intervals exclude zero. For time in range, there are no differences between groups, as the 95 percent confidence intervals include zero.

Efficacy for ONWARDS 6 is summarized as follows. Noninferiority of insulin icodec to insulin degludec was demonstrated both in combination with insulin aspart in treating participants with type 1 diabetes at week 26. Long-term duration of A1c at week 52 nominally favors insulin degludec. Reductions from baseline in A1c for participants on insulin icodec at week 26 and week 52 are observed. Results of secondary endpoints for glycemic efficacy tend to favor insulin degludec.

Dr. Pucino will now review the safety findings for ONWARDS 6.

FDA Presentation - Frank Pucino

DR. PUCINO: I'm Frank Pucino from DDLO. Compared to insulin degludec, there were no meaningful imbalances in deaths, discontinuations due to adverse events, common adverse events

associated with insulin products, or serious adverse events; that is with the exception of an imbalance of hypoglycemia SAEs in the insulin icodec arm.

Hypoglycemia is a known adverse effect of all insulin products and can be life threatening. The treatment goals with insulin therapy are to improve glycemic control while minimizing the risk of hypoglycemia. In ONWARDS 6, an increased risk of hypoglycemia was observed in the insulin icodec arm compared to the insulin degludec arm. When considering the clinical relevance of this finding, it is important to note that newer insulin products such as insulin degludec may be associated with a lower risk for hypoglycemia compared to several other marketed basal insulin products. This product also has a labeling claim for less hypoglycemia than daily insulin glargine in patients with type 2 diabetes.

In ONWARDS 6, hypoglycemia was assessed throughout the study period up to week 57. The definitions for hypoglycemia, shown in blue font on

this slide, are consistent with the 2024 American Diabetes Association guidelines and the 2023 FDA draft guidance. The review of these events will primarily focus on level 2 and level 3 hypoglycemia, also referred to as clinically significant and severe hypoglycemia, respectively. Nocturnal hypoglycemia included hypoglycemic episodes occurring between 12 midnight and 6 am. Hypoglycemic events captured by CGM were to be confirmed by SMPG.

The event rates of overall level 2 or 3 hypoglycemia reported in ONWARDS 6 and captured by SMPG are shown in this figure. Events reported during the 26-week treatment period are shown on the top portion of this slide and during the entire 57-week study period on the bottom. A higher rate of level 2 or 3 hypoglycemia was reported with insulin icodec compared to insulin degludec during both phases of the trial.

The estimated rate ratio for subjects experiencing level 2 or 3 hypoglycemia during the 57-week period, shown on the bottom row of this

figure, was 1.8 with a risk difference of approximately eight more events per patient year of exposure, both favoring the insulin degludec arm. The rate ratios and risk differences for level 2 hypoglycemia and for level 3 hypoglycemia during the main and extension phases of this trial were similar.

Although the protocol for ONWARDS 6 specified that SMPG data should be obtained to confirm hypoglycemic events, FDA draft guidance issued since the conduct of ONWARDS 6 notes that CGM data and SMPG data provide complementary perspectives on the risk of hypoglycemia. The event rates of overall level 2 hypoglycemia captured by CGM during the 26-week and extension study periods are shown on the top portion of this slide and nocturnal level 2 hypoglycemia on the bottom.

Events captured by CGM were higher than those captured by SMPG. The estimated rate ratio for the 24 week plus extension phase was 1.29 for the total level 2 hypoglycemic episodes, with a

risk difference of 20 episodes per patient year of exposure, again favoring the insulin degludec arm. Similar trends were observed for the rate ratios of nocturnal events though the risk differences were less due to lower numbers of these events.

As a reminder, this slide previously presented by Dr. Kenna shows that the maximum glucose lowering effects following a weekly insulin icodec injection occurs on days 2 to 4 and is lowest on days 5 to 7. The rates per hundred patient-years of level 2 or level 3 hypoglycemia -- shown on the Y-axis, by the day of the week on the X-axis -- are depicted in this figure. The observed rates for the insulin icodec and insulin degludec arms are shown as blue and gray bars, respectively.

The peak hypoglycemic rates generally occurred on days 2 to 4 after each weekly injection of insulin icodec, while the rates were similar for each day of the week in the insulin degludec arm. Event rates with insulin icodec were highest on day 3 and lowest on day 7. This finding is not

unexpected based on the observed PK/PD profile of insulin icodec.

The total number of hypoglycemic episodes can be driven largely by a few subjects who experienced a large number of hypoglycemic events. For example, one subject in the insulin icodec arm experienced 34 of 56 severe hypoglycemic episodes, while one subject in the insulin degludec arm accounted for 12 of 25 events. Therefore, a sensitivity analysis was performed to assess the robustness of the results from the applicant's prespecified model.

In this figure, subjects with events refer to the number of subjects with one or more level 2 or 3 hypoglycemic events. The time at risk was defined as the time from the first drug exposure to the first event, while for individuals who did not experience an event, the time at risk was set to equal the on-treatment period.

Results were consistent with the event rate ratio shown on the previous slides that incorporated recurring episodes. Shown in the

bottom row of this figure, subjects in the insulin icodec arm had a 50 percent higher risk of experiencing at least one level 2 or 3 hypoglycemic episode compared to insulin degludec treated subjects. The risk during both the main and extension study periods were primarily driven by level 2 events.

The applicant was asked to provide descriptive statistics for the duration of level 2 hypoglycemia based on CGM, which is presented in this slide. The duration of level 2 events was defined as the period of time from when the interstitial glucose value is less than 54 milligrams per deciliter for at least 15 minutes to when it was greater than or equal to 54 for at least 15 minutes. This definition is consistent with a recent international consensus statement on the use of CGM in clinical trials. Although events of level 2 hypoglycemia were more frequent in the insulin icodec arm, the mean and median duration of hypoglycemia were approximately 40 and 25 minutes, respectively, and similar between arms.

Again, using CGM data, the time spent below glucose range -- less than 54 milligrams per deciliter during weeks 22 to 26, 48 to 52, and 0 to 52 -- are displayed on the Y-axis of this figure in 2-week increments for the duration of the trial, as shown on the X-axis. The blue bars represent the insulin icodec arm and the gray bars, insulin degludec. The observed time below range -- less than 54 milligrams for both treatment arms at weeks 0 to 52 and 48 to 52, but not at weeks 22 to 26 -- met the ADA recommended glycemic goal of less than 1 percent; that is approximately 15 minutes per day. For all three time periods, time below range, less than 54 milligrams per deciliter, was lower in the insulin degludec arm.

In ONWARDS 6, serious adverse events were defined as events which resulted in death, were life threatening, required or prolonged hospitalization, resulted in a congenital anomaly, or were considered an important medical event by the investigator. Besides patient-reported data entered in the e-diary for hypoglycemic events,

investigators were requested to complete an electronic case report adverse event form and a safety information form for hypoglycemic episodes that fulfilled the criteria of an SAE.

More serious adverse events of hypoglycemia were observed with insulin icodec compared to insulin degludec. During the 57-week study period, 9 subjects in the insulin icodec arm experienced 14 hypoglycemia SAEs compared to three in the insulin degludec arm. Insulin icodec was associated with a 4.66 event rate per hundred patient-years compared to one event per hundred patient-years in the insulin degludec arm. SAEs in the insulin icodec arm were associated with more dose reductions and administration of IV glucose and glucagon than in the comparator arm; however, none of the SAEs resulted in treatment discontinuations or study withdrawal in either arm.

In response to the agency's concerns to the observed increased hypoglycemia risk associated with insulin icodec, the applicant proposed labeling revisions to better inform prescribers and

patients about this risk. Relevant labeling proposals included the following: restricting the use of insulin icodec to patients wearing the CGM device with low glycemic variability, that is a percent coefficient of variation less than or equal to 36 percent prior to initiating treatment and without a history of recurring severe hypoglycemia or hypoglycemia unawareness; recommending discontinuing insulin icodec in patients experiencing recurring hypoglycemic events; informing patients and providers that the maximal glucose lowering effect of insulin icodec occurs on days 2 to 4 after each weekly injection; and to consider reducing the bolus insulin dose on these days after each insulin icodec injection.

We will next discuss post hoc analyses conducted to evaluate two of the proposed mitigating strategies; that is use of insulin icodec in type 1 diabetes patients with low glycemic variability and dose modifications to address the increased pharmacodynamic response observed on days 2 to 4.

I will now turn the presentation over to Dr. Jaejoon Song from the Division of Biometrics VII, who will review the exploratory analyses of the proposed percent CV cutpoint.

FDA Presentation - Jaejoon Song

DR. SONG: Good morning. My name is Dr. Jaejoon Song, Senior Statistical Reviewer in the Division of Biometrics VII. The Division of Biometrics VII in the Office of Biostatistics provides statistical review for evaluation of safety.

To assess the applicant's proposal for risk mitigation and their supporting post hoc analysis, we reviewed the applicant's exploratory analysis to assess potential associations between glycemic variability and hypoglycemic episodes. For the subpopulation of type 1 diabetic patients, the applicant is recommending insulin icodec use for patients using CGM with a percent coefficient of variation, a measure of glycemic variability less or equal to 36 percent.

According to published reports, this

glycemic target is associated with a lower risk of hypoglycemia and is discussed by both the American Diabetes Association and the international consensus. In the exploratory analysis to support the applicant's proposal for risk mitigation, subgroup was defined based on percent CV at week 0 to 2 after treatment initiation based on the subject's CGM measurements. Also, exploratory analysis presented in the slides only considered data for subjects with at least 70 percent of planned CGM measurements.

In terms of the analysis methods, the rate of level 2 or level 3 hypoglycemic episodes was calculated for each subgroup. We also calculated the crude rate ratio with 95 percent confidence intervals to assess between arm differences within the subgroups. Additionally, we looked at the distribution of percent CV over 52 weeks study period to examine the consistency of percent CV within the subgroups.

This slide presents the main results from the exploratory subgroup analysis using percent CV

cutpoint of 36, defined using CGM data during the first 2 weeks of treatment. The bar plots illustrate level 2 or level 3 hypoglycemic episodes captured using SMPG by percent CV subgroups during the main and extension phases.

The rate ratios between the two treatment arms within each subgroup are presented above the bar plots. The rate per 100 patient-years of hypoglycemic episodes captured by SMPG were 922 and 2,121, respectively, for subgroups with percent CV less or equal to 36 and percent CV greater than 36 in the insulin icodec arm.

Similarly, the rate of hypoglycemic episodes was lower in the lower percent CV subgroup in the insulin degludec arm. Between arms, however, within each subgroup, the rate ratios indicate that the rate of hypoglycemic episodes were still nominally higher in the insulin icodec arm compared to the insulin degludec regardless of the percent CV subgroup. Specifically, the rate ratio comparing insulin icodec to insulin degludec in subgroup of subjects with percent CV less or equal

to 36 was 1.94, meaning that the rate of hypoglycemic episodes was almost 2 times higher in the insulin icodec arm compared to those in the insulin degludec.

The distribution of percent CV was assessed to understand the consistency during the 52-week study period. The Y-axis in the plot represents percent CV and the X-axis represents time in 2-week intervals. The left panel represents the distribution of percent CV for subjects who had percent CV greater than 36 in the first 2 weeks after treatment initiation during the main plus extension trial treatment period. The right panel represents distribution of percent CV for subjects who had percent CV greater than 36 in the first 2 weeks. The blue boxes represent the insulin icodec arm and the gray boxes represent the insulin degludec. The distribution of percent CV after initiation of treatment appeared to be reasonably stable throughout the trial period within each subgroup.

To summarize, we discussed some exploratory

analyses to evaluate the applicant's argument and potential associations between percent CV and hypoglycemic episodes. The exploratory analyses suggested that lower rates of level 2 or level 3 hypoglycemia were observed in subjects with percent CV less or equal to 36 at week 0 to 2 after treatment initiation; however, within the percent CV subgroups, the rate of level 2 or level 3 hypoglycemic episodes were still numerically higher in the insulin icodec arm compared to the insulin degludec regardless of the percent CV subgroup. Descriptive analysis suggested that after initiation of treatment, subjects percent CV appeared to be generally stable over the 52 weeks main plus extension study treatment period in both insulin icodec and insulin degludec arms.

Lastly, we would like to point out some statistical issues of the subgroup analyses. The first point that we would like to make is that the applicant's subgroup analyses was based on a post-baseline variable using percent CV calculated based on CGM measurements in the first 2 weeks

after treatment initiation. A subgroup defined on post-randomization feature might potentially be influenced by the treatment itself. While the distribution of percent CV after initiation of treatment appeared to be reasonably stable throughout the trial period, the stability of percent CV in relation to pretreatment percent CV could not be examined within this database because there were no baseline CGM or SMPG measurements.

The second point that we would like to make is that the choice of variable to define the subgroup was post hoc. In search for a subgroup with potentially lower risk of hypoglycemia, the applicant reported that they have explored a multitude of variables.

Lastly, the applicant's proposal for risk mitigation in type 1 diabetic patients suggest restricting the use of insulin icodec to patients wearing a CGM device with percent CV less or equal to 36 prior to initiation of insulin icodec treatment. The applicant's assumption is that the pretreatment percent CV levels will be comparable

to percent CV levels after initiation of treatment; however such assumption cannot b e examined within this database.

I will now turn the presentation over to Dr. Elyes Dahmane, who will discuss pharmacometric modeling of alternative dose titration strategies.

FDA Presentation - Elyes Dahmane

DR. DAHMANE: Hello. My name is Elyes Dahmane. I'm the primary pharmacometrics reviewer for this application. I'm going to share the exposure-response modeling results investigating whether alternative dose titration schedules of insulin products could reduce level 2 hypoglycemia and maintain glycemic control.

In study ONWARDS 6, the insulin icodec dose was uptitrated or downtitrated based on the lowest pre-breakfast fasting plasma glucose measured on days 5 to 7; in other words, the last 3 days of the dosing interval. The question being investigated by exposure-response modeling is whether titrating the dose of insulin icodec, based on the fasting plasma glucose of alternative days than days 5 to 7

will reduce the incidence of level 2 hypoglycemia and maintain acceptable efficacy.

Using a modeling approach, three titration scenarios were simulated. The first scenario is weekly titrating insulin icodec based on the lowest fasting plasma glucose of days 2 to 4. The second scenario is titrating insulin icodec based on the lowest fasting plasma glucose of days 3 to 5. The rationale for choosing days 2 to 4 or days 3 to 5 for alternative titration is that the maximum glucose lowering effect of insulin icodec is observed during these days and the incidence of hypoglycemia is higher as well during these days. Finally, the last simulated scenario is to maintain the insulin icodec titration unchanged as studied in ONWARDS 6, but reduce the dose of bolus insulin on days 2 to 4.

In this table, I will summarize the outcomes at week 26 for the fasting plasma glucose A1c and the rate of level 2 hypoglycemia under the different titration scenarios. Values in the tables are means and 95 percent confidence

intervals. The first row of the table shows the observed data from study ONWARDS 6 with an A1c level at week 26 of 7.15 percent, a change from baseline in A1c of minus 0.47 percent, and a rate of level 2 hypoglycemia of 19.9 patient-years of exposure.

The second row shows not the observed but the model predicted outcomes from the studied dose titration scenario in ONWARDS 6. As you can see, the model predictions are matching the observed results in the first row, suggesting that the model is able to replicate the observed data and can be used to perform predictions.

The third and fourth rows of this table show the predicted results for insulin icodec dose titration based on the lowest plasma glucose of alternative days; here either days 2 to 4 or days 3 to 5. If you look at the last column, the rate of hypoglycemia for both alternatives, the model predicts a decrease in hypoglycemic events compared to the study titration, with about 30 percent decrease in hypoglycemic events from 21.2 to around

15 patient-years of exposure.

Although we predicted decrease in the rate of hypoglycemia with days 2 to 4 or days 3 to 5 titration scenarios, these scenarios were predicted to result in high A1c levels at week 26 of about 7.6 percent with no change from baseline in A1c levels.

Finally, the last row of the table shows the outcome from the simulation scenario in which the studied insulin icodec titration is unchanged, but instead, the dose of bolus insulin is reduced by 30 percent on days 2 to 4 of each dosing interval. According to this scenario, the hypoglycemic events decreased compared to the studied titration by about 40 percent, from 21.2 to around 12.7, which is comparable to what was observed in the insulin degludec control arm in ONWARDS 6.

The predicted A1c at week 26 of 7.27 percent and the change from baseline in A1c of minus 0.37 percent are comparable to the values observed in ONWARDS 6, and therefore, this suggests no compromise in glycemic control.

The main conclusion that can be drawn from these results are that titrating the dose of insulin icodec based on the lowest fasting plasma glucose of alternative days than days 5 to 7 is predicted to reduce the rate of hypoglycemia but will compromise the glycemic control. The last option of reducing the dose of bolus insulin by 30 percent on days 2 to 4 was predicted to reduce hypoglycemia and maintain glycemic control.

I will now turn the presentation over to Dr. Frank Pucino, who will provide a summary of safety and approaches to patient management.

FDA Presentation - Frank Pucino

DR. PUCINO: I'm Frank Pucino from DDLO. I will now briefly summarize the benefit-risk and proposed mitigation strategies. Insulin icodec was determined to be noninferior to insulin degludec at week 26 in ONWARDS 6. Weekly administrations of insulin icodec could decrease the number of basal insulin injections from 7 to 1 per week. Results of secondary glycemic endpoints tend to favor insulin degludec. Due to multiple limitations, the

results of the DTSQs analysis cannot inform whether subjects were more or less satisfied with insulin icodec compared to insulin degludec.

In ONWARDS 6, there were no meaningful imbalances between arms and deaths, discontinuations due to adverse events or SAEs, excluding hypoglycemia; however, at week 57, insulin icodec was associated with a 50 percent higher incidence and an 80 percent higher event rate, clinically significant or severe hypoglycemia, compared with insulin degludec.

Higher rates were observed regardless of whether hypoglycemia was captured by SMPG or CGM. The risk was greatest on days 2 to 4 following weekly injections, coinciding with insulin icodec's peak glucose lowering effect. The observed risk is consistent with a higher percent CGM-based time below range in the insulin icodec arm. Hypoglycemic events were similar between arms in duration, management, and recovery.

Exploratory analysis assessed whether patient selection could mitigate the risk of

hypoglycemia. Selecting patients with a CV less than or equal to 36 percent could potentially reduce the hypoglycemia risk of insulin icodec to be comparable to the overall population in the insulin degludec arm; however, within identical percent CV subgroups, the risk of hypoglycemia was always higher in the insulin icodec arm. No data were provided to confirm that percent CV during the first 2 weeks of treatment is representative of the percent CV on the previous basal insulin therapy.

Pharmocometric modeling assessing changes to basal and bolus components predicted that alternative basal titration approaches reduce the risk of hypoglycemia of compromised efficacy. In contrast, 30 percent reductions in bolus insulin dosing on days 2 to 4 maintained glycemic efficacy and optimized safety; however, no clinical studies were conducted to confirm that patients could successfully titrate bolus insulin differently on specific days of the of the week without increasing medication errors.

This concludes our presentation. We would

now be happy to address any clarifying questions and look forward to receiving input from the committee on the discussion points of this meeting. Thank you.

Clarifying Questions to FDA

DR. LOW WANG: Thank you so much for your presentation.

We will now take clarifying questions for the FDA. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I'd like to ask the first question. I wanted to see if you could please pull up slide 46. One thing I noticed is that there -- and this is kind of actually looking back at the FDA briefing booklet, table 17, which is on page 55 -- were 13 participants in the icodec arm and 7 participants in the degludec arm who had discontinued the study. And then when we look a little bit further to compare the differences in discontinuation of treatment, it was about double in the icodec arm, whether it was the main study or the extension.

In terms of reasons for discontinuing the treatment, hypoglycemic episode accounted for very few, so 1 versus 0, but if you look at the reasons for other -- because this is the largest number of participants discontinued for some other reason -- there were several that were related to glucose controls, so hypoglycemia, glycemic variability, unpredictability of the insulin. So if you actually added those in, it would have been maybe 8 participants in the icodec arm and zero in

the degludec arm who discontinued the treatment because of concerns about hypoglycemia or other glucose-related issues.

Now, looking at slide 46 and focusing on the SAEs of hypoglycemia, I think one of my questions here is what was the breakdown of the serious criteria for the hypoglycemia? Because we can see here that there is definitely a numerically higher number of subjects, as well as number of SAEs related to hypoglycemia in the icodec arm, and thinking about burden for our patients -- hospitalizations, ER visits et cetera, aside from the treatment of the hypoglycemia -- I was wondering if the FDA could give us information about the breakdown for what made these episodes serious.

DR. NGUYEN: Thank you. Dr. Pucino will answer this question. Please bring up slide 151.

DR. PUCINO: Slide 151, please. Hopefully, this provides the information you're interested in. These are the patients in the insulin icodec arm that experienced SAEs, and these are the 9 patients

and the 14 events. Basically, the preferred term, MedDRA preferred term, that was used to report these events was "hypoglycemia," yet if you look on in the section under action, you'll see that loss of consciousness was not uncommon with some of these events.

DR. LOW WANG: Thank you. I think it's a little bit hard for me to tell. So these met serious criteria because of hospitalizations, ER visits. What were the --

DR. PUCINO: Yes. Typically, these are hospitalizations with loss of consciousness, emergency physician visits. The first three were reported as emergency physician visits, four patients needed IV glucose, five had the dose reduced, but two also required glucagon administration.

DR. LOW WANG: Okay. Great. Thank you.

I'd like to move on to Dr. Brittain.

DR. BRITTAIN: Erica Brittain. Thank you. My question relates to slide 66, which was a summary slide, if I have that number right. Yes,

it's about that last part, about the questionnaire.

As we've seen before, there's some suggestion that the results were somewhat worse in the once-weekly arm for the survey results, but this slide seems to be saying it cannot be informative. So is the point being made here is that you don't think that the questionnaire is of value to consider?

DR. NGUYEN: I'm going to invite Dr. Daniels to come up. In the meantime, can you please bring up slide 105?

DR. DANIELS: Thank you. My name is Selena Daniels, Deputy Director in the Division of Clinical Outcome Assessment. Actually, can we pull up slide 106? Thank you.

The issue here is we're not saying that the DTSQ is not informative, but the data itself is difficult to interpret for a number of reasons, the first reason being that the DTSQ assesses satisfaction of the patient's current treatment. In this particular case, in ONWARDS 6, participants were taking more than one current treatment in a

trial, so it's difficult to know if they were satisfied with icodec or the product that they were on. It's also unknown whether the components of the treatment and satisfaction in DTSQs are adequately assessed based on patient and clinician input, meaning if it's comprising all components of satisfaction that is meaningful to patients in this particular context.

In addition, the DTSQs was administered at baseline, week 26, which was the primary timepoint at the secondary endpoint in week 52. We don't know if we were missing important information between baseline and week 26, and knowing whether the trends of the satisfaction were moving in the right direction all along through week 26 or if it could have dipped or whatnot. It's also unknown what a meaningful score change is in the DTSQ Treatment Satisfaction score.

And lastly, there are limited details with regard to the methods in terms of whether the tool itself was translated and culturally adapted appropriately. So in the absence of that, we don't

know if it's fit for purpose for the intended populations in these multinational trials.

DR. BRITTAIN: Thank you.

DR. LOW WANG: Thank you.

Dr. Crandall?

DR. CRANDALL: Yes. Jill Crandall. Actually, my question was exactly the same, so it's been answered. Thank you.

DR. LOW WANG: Okay. Thank you.

Dr. Kalyani?

DR. KALYANI: Thanks. Rita Kalyani. I had a question about slide 31, and it was in regards to the change in A1c at week 52, comparing insulin icodec to insulin degludec. In contrast to week 26, where we saw that the A1c differences were more comparable, in this one, icodec had a 0.38 percent reduction versus 0.52 percent reduction. And I was curious how the methodology for multiple imputation, the return to base methodology, and the number of missing data at week 52 may have impacted the results here, and whether what we're seeing may reflect more missing

data potentially in the icodec arm versus the degludec arm.

DR. NGUYEN: Dr. Crackel, would you like to take that?

DR. CRACKEL: Thank you for the question. The results for week 52 are based on the return to baseline methodology. There's some more missing data at week 52 which was expected. We did consider the results at week 52. Even though the lower bound of the confidence interval is greater than zero, we considered that to be exploratory and not confirmatory.

Does that answer your question?

DR. KALYANI: Yes. I guess I was wondering if we would see more of a convergence towards zero just because there is still missing data. And I think that answered it, with the lower confidence interval kind of bordering zero, it sounds like this is more an exploratory analysis from what you're saying; is that correct?

DR. CRACKEL: Yes.

DR. KALYANI: Alright. Thank you so much.

DR. LOW WANG: I don't see any other panel members with raised hands. I did want to ask about slide 11, if we could bring that up.

In this slide -- and we've seen different forms of this -- it looks like by day 7, the fraction of the weekly area under the curve for the glucose infusion rate for day 7 is only 8.7 percent compared to what would be around 14 to 15 percent if the pharmacokinetics was even across the entire week. So I was wondering if the FDA could comment about this marked difference. It's about a 40 percent lower area under the curve here.

DR. NGUYEN: Can you please clarify that question?

DR. LOW WANG: Yes --

DR. NGUYEN: Is that a clinical question or is that more of a methodology?

DR. LOW WANG: Sorry. I guess clinical question. So just thinking about the clinical impact of this marked reduction in -- or the marked, I guess, increase in glucose infusion rate. I guess it would be a reduction by day 7 because of

the difference in pharmacokinetics over the course of 7 days.

DR. NGUYEN: So the question, I'll repeat it, to help Dr. Pucino.

Dr. Yanoff is going to answer this question.

DR. YANOFF: Dr. Low Wang, I think that, clinically, this is alluded to in the other talks, in that this pattern is probably what is driving the hypoglycemia observations that we're seeing for icodec versus degludec. I believe we showed a slide showing that the hypoglycemia, the pattern tended to occur on the same days where the GIR was higher.

So if you're talking about a question about the clinical relevance for safety, I think that's primarily related to the hypoglycemia, which the data do suggest reflect this variability. I know in the clinical trials, there was some effort on behalf of the patients to mitigate this by self-adjusting their bolus insulin, and one of the additional strategies that's been proposed by the applicant is to try to do that a little bit

further.

As far as efficacy, we do look at A1c to assess whether a product is providing glycemic control. So as far as A1c, you're not really seeing this reflected in the glycemic control, but if we looked at day-to-day glycemic values in CGM, you might see some higher values on day 7, but I would have to defer back to the team to comment on whether those higher values were clinically concerning or whether they were just staying at the higher end of the normal range; so I'll turn it back over to the clinical team.

Did that answer your question?

DR. LOW WANG: Yes. Thank you. My question was specifically that last part that you mentioned, which is do we have -- I guess now I've clarified my question, which is do we have CGM data that shows that there is less efficacy or more hypoglycemia on day 7 because of this difference in pharmacokinetics through the course of the week?

DR. YANOFF: Okay. My team is flagging for me that Novo Nordisk may have a slide and that was

shown in their presentation. If we could pull that up again, that would go over that point.

DR. LOW WANG: Okay. I'd like to invite Dr. Gough to answer the question.

DR. GOUGH: Yes. Thank you.

Towards the last part of that question, you were asking about CGM data and the efficacy towards the end of the week. What I can show you here on slide CO-48 is CGM data in type 1 diabetes over the 7-day period, and what you can see is that the CGM data over that period is reassuring in that insulin icodec is very similar to insulin degludec. And you can see if we look at the mean CGM measured glucose over a week, it's not just similar to insulin degludec, but also, for most of the time, below the 180-milligram per deciliter threshold for glycemic control.

So we would argue that this supports the benefit that we see with insulin icodec and supports the noninferiority with respect to the A1c.

DR. LOW WANG: Okay. Terrific. Thank you.

Next, I'd like to call on Dr. Dutta.

DR. DUTTA: Hello. Sandeep Dutta. My question is regarding slide 51. I'll proceed with the question. It's a two-part question.

First is, how easily is this percent CV data available for the prescriber to act on; how convenient it is? And the second part is, while the related risk is a little bit higher, there's a small difference in relative risk between the percent CV. Is that a clinically meaningful strategy to use the percent CV for risk mitigation for hypoglycemia?

DR. NGUYEN: I'll have Dr. Pucino answer the first part, and then I'll have Dr. Song answer the second part.

DR. PUCINO: For the first part, particularly for the Dexcom G6 that was used for this trial, it will report the ambulatory glucose profile, and based on that, it will give you the percent CV with that, as well as all the other measurements. So it should be readily available to prescribers and patients.

DR. DUTTA: Thank you.

DR. PUCINO: Does that answer the question?

DR. DUTTA: Yes. Thank you.

DR. LOW WANG: Thank you.

Next, Mr. Tibbits.

DR. NGUYEN: Actually, hold on. Can you also bring up slide 137 to reinforce that point that Dr. Pucino made? This is a standard ambulatory glucose profile that comes out of a CGM. You'll see there towards the middle that there's a variable glucose variability there.

DR. DUTTA: And the second part of my question was how meaningful is it as a risk mitigation strategy?

DR. NGUYEN: Can you please repeat the question, the second question, please?

DR. DUTTA: Yes. How meaningful is it for clinical practice to use that percent CV as a risk mitigation strategy to limit hypoglycemia?

(No audible response.)

DR. GOUGH: Okay. Thank you.

DR. LOW WANG: Actually, just a quick

question. Would the FDA like to respond to that question?

DR. NGUYEN: We're trying to find the correct slide to answer that question.

(Pause.)

DR. NGUYEN: Please raise slide 157.

DR. SONG: Dr. Jaejoon Song. This is the same information that we provided in previous slides, but in the table and above the bar plugs, we included the risk difference, and crude, and the 95 percent confidence interval for the risk difference. And as you can see for the percent CV subgroup of less or equal to 36 percent, there were approximately 4.5 additional level 2 or level 3 hypoglycemic events per person-years, and the confidence interval excluded zero.

DR. DUTTA: So the difference between the two groups of about 3 is clinically meaningful for the prescriber.

DR. NGUYEN: Dr. Archdeacon will be taking this question.

DR. ARCHDEACON: I think the slide that

we're showing, the risk difference, that's based on the SMPG, so there we're seeing a difference of about 3.

My statistical colleagues, do we have the risk difference for if it was based on CGM? I think slide 161; this is the same slide, I think. Did we calculate the risk differences based on CGM data? 158, please?

So here, the risk differences for the overall population appears to be 18. With the risk mitigation strategy, it reduces to 2, so that would argue, based on the CGM data, that that was a reasonably potent risk mitigation strategy. Based on the SMPG data, I think we saw less effect of that risk mitigation strategy.

DR. DUTTA: Thank you. That answers my question.

DR. LOW WANG: I would like to move on to Mr. Tibbits.

MR. TIBBITS: Thank you. Paul Tibbits. This is maybe more of a flag than a question, but, Dr. Low Wang, the question you asked earlier I

flagged as a note for me to raise and may be more appropriate for discussion.

I still feel like maybe even if clinically we don't have an answer from the data right now, I still think from a patient perspective we need to think about exactly what you noted, which is what is the impact on patients in terms of having to do additional calculations based on the day of the week, based on the profile of the basal insulin?

So if we see such a dramatic reduction of, potentially, impact on day 7, even if the CGM numbers look the same, I'd be interested to see if we know they remain looking the same because a patient's boluses have increased by 10, or 20, or 30 percent on those days. So I still don't know that we have a full picture of what seems to be a pretty dramatic downturn at the end, even though this discussion has largely focused on what's happening on days 2 to 4. I think what's happening, at least on that graph, also seems relatively dramatic from the day in the life of a patient's perspective.

DR. LOW WANG: Thank you for that comment. I do think that in terms of multiple insulin dose adjustments, it could be potentially problematic.

So I'd like to move on to Dr. Crandall.

DR. CRANDALL: Yes. Jill Crandall. Actually, just following up on the the comment just made by Mr. Tibbits, I thought that we were shown a slide that showed time in range on each day of the week of the dosing interval, and I thought that was informative. I don't recall what the number was. We just saw a slide looking at the mean glucose levels by day of the week or dosing interval, but I thought we also saw time in range, if that's available.

DR. NGUYEN: Thank you. Yes, I think that slide came from the applicant.

DR. LOW WANG: Yes. Novo Nordisk, please go ahead and respond.

DR. GOUGH: Yes. If it would be helpful, I can show you the slide that I showed earlier, which shows the percentage time in range for each day of the week, and you can see on day 7, we have a time

in range of over 56 percent, which admittedly is lower than earlier in the week on days 2 and 3, but it still shows a high proportion of time of patients within target glucose range.

DR. CRANDALL: Thank you. This is the slide I was referring to.

DR. LOW WANG: Thank you.

Moving on to Dr. Brittain.

DR. BRITTAIN: Yes. Erica Brittain. I am trying to understand why the results are somewhat different with the CGM. The results with respect to hypoglycemia are somewhat different with respect to the CGM results and the self-monitoring results.

Does anyone want to speak to that? I know the study is not blinded, and if I'm understanding correctly, the self-measurements are done based on someone deciding they need to do it. And the study's not blinded, so I don't know if that could have any potential explanation for why the results seem somewhat different.

DR. NGUYEN: I'll ask Dr. Pucino to answer this question.

DR. PUCINO: Excellent question. There are a couple different reasons. One is, as you mentioned, the open-label design could have influenced how often the SMPGs were checked. Doing SMPGs is a manual assessment. Patients when they became hypoglycemic were supposed to measure every 15 minutes until the blood glucose went above 70.

So there were all of those caveats for why you might not have as many events, and once you get to CGM events, there were enough events that things seem to improve a little bit better, but personally I feel that they're complementary of each other, and they're both suggesting that things are going in the same direction no matter what, but you're dealing with a lot more events when things are done by CGM, basically.

DR. BRITTAIN: Can I follow up just a moment on that? When you say they're complementary, what do you see as the advantage of the self-report versus the CGM?

DR. PUCINO: I think the self-report, the device that they use could measure blood glucose

values down to 10 milligrams per deciliter with the Accu-Chek, so I think that's part of it. Actually, when I say complementary, we do see things coincide. If you're getting a 4-point SMPG with a CGM, there is a lot of correlation between the two, so I think they provide you some of the same but also some different information on that.

DR. NGUYEN: I'm going to invite Dr. Yanoff also to answer that question.

DR. YANOFF: Thank you, Frank.

I think there's one point that wasn't mentioned. SMPG are finger sticks, and the glucometers tend to be more accurate than the CGM, historically. That has really been the main advantage to SMPG until now. CGMs are now getting to a point where they're more accurate, and there are a couple that are approved to replace SMPG for patient management, and the one that was used in this clinical study is, I believe, one of those. So we do believe it's reliable enough to assess hypoglycemia in this study, but SMPG is still considered more reliable, but it has its

disadvantages in that it requires patient effort, it can't measure hypoglycemia at night, and it's generally prompted by symptoms.

So given that hypoglycemia unawareness is a common problem, you might miss those episodes as well. The CGM is probably giving you a broader picture of what we're seeing with this drug with the caveat of the accuracy in the low end of the range of the device. But given that all patients use the same device, I think it's as reliable as we can expect with the best of the current technology.

DR. BRITTAIN: Thank you.

DR. LOW WANG: So we're just a little bit overtime before we're supposed to break for lunch, but we have two more panel members with questions, so we'll shorten our lunch slightly.

Mr. Tibbits?

MR. TIBBITS: Thank you. Paul Tibbits.

Dr. Brittain, I just wanted to respond very quickly from a patient perspective currently on CGM and having used self-monitoring as well. I think all the comments that preceded mine are exactly

right. I think a lot of it is self-monitoring is often precipitated by a feeling that something may be happening, so whether you're going up or you're going down, in this case, hypoglycemia. So it's more of a snapshot and you don't know until you monitor.

With the CGM, you have the advantage of having trend arrows, so if I have a blood sugar at 120 and it's trending down, and I can see it's been going from 140 to 120 and potentially still trending down, I have the ability to take action then and potentially prevent ever getting to hypoglycemia versus self-monitoring, which I may not feel something until 70 or 65, at which point I've already entered into hypoglycemia, so I think that probably explains part of it. And I would note that the comment from the last FDA presenter was exactly right, that both the Dexcom G6, and now G7, based on FDA approval, both no longer require calibration by self-monitoring mechanisms.

DR. LOW WANG: Great. Thank you.

One last question before we break for lunch,

and I'll ask you to be brief and state your name for the record.

Dr. Crandall?

DR. CRANDALL: I recall that the distribution of the cohort is relatively mostly Caucasian, but I wonder if there are any racial or ethnic differences observed in the frequency of hypoglycemia with the two treatments.

DR. NGUYEN: I'm going to ask Dr. Pucino to answer that question.

DR. PUCINO: Yes.

DR. NGUYEN: Please bring up slide 18. Sorry.

DR. PUCINO: What's that?

DR. NGUYEN: Sorry. Please bring up slide 18 to help him.

DR. PUCINO: First of all, you're absolutely correct; the distribution by race was somewhat skewed to the Caucasian population. But with that being said, the populations that were enrolled -- actually, even for the black, African American, population -- in the trial itself were

comparable to what you might see in the diabetic population, but we do see lower numbers.

We had asked the applicant -- and maybe they can respond also -- to look at subgroups that were responsible for people having more recurrent events in this trial, and based on the analyses that they did for the subgroups, there didn't appear to be a difference, although we are dealing with some relatively small numbers to be able to tell that. I don't know if Novo Nordisk could address that also with the analyses that they did for subgroups.

DR. LOW WANG: I'd like to ask Novo if they'd like to respond to that request.

DR. GOUGH: Yes. I can just confirm the previous comments. We did perform a subgroup analysis. The numbers were small, and there's no appreciable differences between different groups, and certainly between whites, Asians, and the black or African Americans. There's consistency in results across the program, across the study.

DR. CRANDALL: Okay. Thank you.

DR. LOW WANG: Thank you. I did see one

more raised hand from Dr. Onumah, and I'm hoping that after the open public hearing, we'll have time to take more clarifying questions, if we have time.

So we will now break for lunch and reconvene at 1:15 Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene at around 1:05 pm to ensure you're connected before we reconvene at 1:15 pm. Thank you.

(Whereupon, at 12:43 p.m., a lunch recess was taken, and meeting resumed at 1:15 p.m.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

Open Public Hearing

DR. LOW WANG: Welcome back. We will now begin the open public hearing session.

Both 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 applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have 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 for 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.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

You have five minutes.

MS. HEVERLY: Good afternoon. I'm Julie Heverly. The first time I took an insulin injection, I passed out in my doctor's office. Diagnosed with type 1 during college, my body reacted this way to shots for weeks. Up to 6 shots a day, 7 days a week, I had to be monitored like a toddler while dosing each life-saving injection.

Fear of needles is real for many, including those of us living with diabetes. That fear can be a barrier to proper and effective diabetes management. If a once-weekly dose of insulin had been available 25 years ago, I would have begged for it; and then, like every time I change an aspect of my management plan, I would have worked with my care team to monitor and adjust therapy to reduce the risk of adverse reactions. Innovation is essential to the health, well-being, and the survival of the 8 million Americans who rely on insulin.

My personal health journey has led me to serve as the Senior Director for the diaTribe

Foundation, a nonprofit dedicated to ensuring that people with diabetes have the resources and education needed to thrive. I have not received any support from the sponsor related to my remarks. diaTribe does receive funding from Novo Nordisk, other pharmaceutical and device companies, and various supporters of our mission. My remarks today, and those that we submitted, are those of diaTribe alone.

My life has been dramatically improved by the evolution and availability of insulins, pumps, and continuous glucose monitors, but even with those advances, diabetes is unpredictable. There are 42 factors that affect glucose levels. Trying to manage diabetes remains a challenge for millions. If you have seen one person with diabetes, you have seen one person with diabetes. It is an insidious, progressive condition. Continued innovation and options that provide more therapeutic flexibility are critical to meet our individual needs.

For many people with diabetes, the fear of

needles and injections, developing scar tissue, and the inconvenience and difficulty of injecting insulin affects our ability to manage our disease. This is not just anecdotal, but documented in published studies noted in our written comments. Once-weekly dose insulin has the potential to improve insulin adherence, which will in turn improve quality of life and health outcomes.

Weekly insulin may have particular benefits for certain groups of patients such as people in long-term care facilities. It also has the potential, if accessible, to reduce health disparities for those who don't have employment or living arrangements. It allows them the flexibility to test their glucose and dose insulin frequently.

This advancement, along with access to CGM, can help ensure that diabetes is better managed and individuals can stay within their targeted glucose range as long as possible. This is time in range, and its many ranges provide clinicians and people with diabetes real-time information of day-to-day

glycemic patterns not reflected by A1c. Millions of us use this hundreds of times a day to make activity, insulin, and nutrition adjustments that minimize highs and lows and allow us to thrive despite diabetes.

To make sure that regulatory decisions support this amazing advancement in diabetes care, diaTribe advocates for CGM-derived time-in-range data to be included by FDA in drug labels. We urge FDA to maximize the use of time-in-range data in the label for insulin icodec, if approved, to the fullest extent supported by the sponsor's application. We also appreciate that not every medical advancement is appropriate for every person with diabetes and look forward to consideration by the committee, FDA, and the sponsor on ways to ensure benefits outweigh the risks for specific populations.

diaTribe is committed to ensuring people with diabetes have the information they need to make life easier. We applaud and encourage therapeutic innovation, such as weekly insulin,

while also promoting essential access to these new therapies that allow us to live and thrive. The voices of people with diabetes must be heard when discussing advances in therapies and technologies that directly affect our lives. As a human being who often feels like my life is a daily science experiment with diabetes, I thank you very much for considering new tools that lessen this burden and for the opportunity to share these statements.

DR. LOW WANG: Thank you.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 please begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 10 minutes.

DR. ABUDAGGA: Thank you for the opportunity. My name is Azza AbuDagga. I'm a Health Services Researcher with Public Citizen's Health Research Group, and we have no financial conflicts of interest. I'm going to start off by a summary based on the FDA briefing document, a summary of the benefits and hypoglycemia risks for

type 1 diabetes for insulin icodec users, and that was based on the ONWARDS 6 only trial, which is the only phase 3 trial done in type 1 diabetes. Then I'm going to also summarize a few things that we gleaned from the literature, which, understandably, the FDA document did not include all aspects, but we thought there are other aspects that should be considered.

Starting off, based on the ONWARDS 6 trial, the findings of that trial, according to the FDA and the published articles for that in the literature, the new treatment was noninferior to insulin degludec, which is a proven daily basal insulin, in terms of lowering the mean changes in A1c at week 26 of follow-up; however, according to the FDA, at week 52 follow-up, the reduction actually numerically favored insulin degludec.

In terms of the promised improved patient outcomes with this newly once-weekly dosing, the FDA concluded that there's no sufficient evidence to support the claim for a higher patient satisfaction for this drug.

In terms of the hypoglycemia risk, the FDA in the briefing document mentioned that at week 52, icodec was associated with up to 80 percent more clinically significant or severe hypoglycemia events compared with the once-daily degludec. So these higher rates with hypoglycemia with this new product was associated with a higher rate of hypoglycemia related adverse events, and the hypoglycemia rate with icodec also coincided with days 2 and 3, which directly coincides with the peak glucose lowering effect of the drug. Interestingly as well, the hypoglycemia rate with this new drug was not exclusively associated with the loading dose or limited to the early titration phase at the start of treatment.

So it looks like the briefing document and the discussion so far has been framed in a way, for a lack of a better term, to find a niche market for the diabetes 2 population, by virtue that there has been exploratory post hoc analyses -- which is the focus of the discussion, mainly -- which have used the percent coefficient variation, which as I

gathered from the discussion earlier today was not available at baseline for subjects in the ONWARDS 6 trial.

Also, they're proposing to limit its use in diabetic patients with type 1 diabetes without a history of recurrent or severe hypoglycemia or hypoglycemia awareness, which is common in the elderly. Also, the continuous use of glucose monitoring seems to be a requirement for the label for the drug, and also there's consideration for alternative dose titration strategies for a bolus injection during days 2 and 3 of the weekly icodec injections, which were not tested in clinical trials.

So we have issues with this approach, and I think these issues also have been noted by the FDA as well. First of all, to be clear, ONWARDS 6 trial excluded individuals with comorbidities or hypoglycemia unawareness, limiting generalizability, and also we cannot in good conscience make explorations based on these trials. Instead, the FDA should require Novo to conduct a

new trial that addresses these new assumptions and concerns raised by the agency.

Also, the agency shouldn't rely on simulation models or post hoc analyses and exploratory analyses for the approval of drugs. That shouldn't be a standard for diabetes drugs, or any drug, really, that affects millions of people, because if we do that, we're going to let real-world experience be the arbitrar of the safety, and that's not really acceptable given the hypoglycemias that we're talking about.

Other issues with the FDA approach is the consideration of the fact that icodec is not peakless, the proposed weekly dose that applies to type 1 diabetes, and also there's no reason to believe that it doesn't apply to type 2 diabetes, so that should be taken into consideration. Also, we have to keep in mind that all of us as patients affected by this the disease -- treating physicians, scientists -- we all know that other factors such as fasting, exercise, illness, infections, hormones, surgery, to name a few, all

of these factors pose challenges for icodec dosing and the effect of frequency and intensity of hypoglycemia. I haven't seen any evidence that these factors were investigated in clinical trials.

Also, hypoglycemia was not studied as a primary outcome in any of the six ONWARDS trials; therefore, according to the published articles of those trials, they acknowledge that any lack of statistically significant differences between hypoglycemia and the comparator basal insulin for type 2 diabetes trials do not necessarily reflect a lack of clinical effect.

Issues that were not raised in the FDA document -- understandably because it was limited in the scope that they chose to focus on -- we should keep in mind that the open-label design used on five of the six ONWARDS trials may have impacted the dosing and monitoring of hypoglycemia adverse events across these trials altogether, or five trials. And also, specifically for ONWARDS trial 6 that has been emphasized by the FDA and the sponsor as well, and I'm quoting here from the article,

"Because participants were permitted to adjust their bolus dose without input from a trial investigator, the knowledge of which treatment they were receiving could have affected any dose adjustments," and consequently the conclusions seemed to have favored icodec for the primary outcome.

Also, the higher satisfaction claim for icodec was not adequately supported. In fact, in ONWARDS 6 -- I'm quoting here also from the article -- "there was a statistically significant treatment difference in favor of degludec in the overall treatment satisfaction score from baseline to weeks 26 and 52."

Other concerns from the literature, there was modest weight gain among icodec users in ONWARDS 2. Also, in ONWARDS 3, there was a higher rate of diabetic retinopathy in that trial among icodec users. There are also evidence of immunologic events, neutralizing insulin antibodies that haven't been adequately tested. We'd be interested to find information about that.

Hypersensitivity is a real challenge, and we also need to have more information about that before making any decisions about this drug. Also, there's missing information for pregnancy/lactation and people who are 75 or older who are not represented in clinical trials.

Other considerations, the utility of the proposed dosing changes cannot simply be extrapolated from the current once-daily treatments without empirical testing; and also the second point that I have here, and I've taken from the American Diabetes Association, they say simple and well-evidenced titration regimens for insulin products is needed, so we cannot really use complex treatment regimens here.

Also, long-term studies lasting more than one year are needed to assess diabetes and cardiovascular outcomes related to icodec relative to the proven daily basal insulins. Also, information regarding the use of this drug in the hospital setting is missing -- there are no studies in the literature about that -- and clearly the use

of this drug is useless for people who use automated insulin delivery systems.

Also, we cannot in clear conscience speak about this drug without mentioning the fact that Novo has chosen to discontinue its older proven daily basal insulin, detemir, shifting its marketing strategy towards insulin icodec to force as many diabetes patients as possible to switch to its more lucrative icodec.

So in conclusion, diabetes patients wouldn't be served. I understand all the frustration out there, the adherence to injections, and the convenience of daily dosing, but a premature approval of an inadequately tested insulin is not going to be of service to diabetes patients. Also, as Public Citizen, we urge the advisory committee to vote no on the question regarding whether the applicant demonstrated that the benefits of insulin outweigh the risks for improving glycemic control in type 1 and also for type 2 diabetes because these are not immune to the same factors here.

So finally, we urge the FDA to set a high

bar for approving ultra long-term insulin by requiring new clinical trials to address the issues that have not been resolved so far, and that's important given that there are at least two more similar drugs in the pipeline. Thank you for the opportunity to comment today.

DR. LOW WANG: Thank you so much.

Speaker number 3, please unmute and turn on your webcam. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

DR. DANNE: Good afternoon. My name is Dr. Thomas Danne. I'm the Chief Medical Officer of JDRF International, the leading charitable organization funding type 1 diabetes, T1D, research, with a mission to accelerate life-changing breakthroughs to cure, prevent, and treat T1D and its complications. By way of disclosure, prior to becoming JDRF's chief medical officer, I received study support and honoraria for advising Novo Nordisk during their icodec

development. JDRF does not have any financial disclosures.

My comments today will focus on two key topics, the substantial burdens and unmet needs that still exist for those living with T1D and how once-weekly insulin formulations can help to meet these needs and alleviate some of the burdens of the disease.

While technologies to administer insulin and continuously monitor glucose have significantly improved, there is no set-it and forget-it treatment currently available for T1D. As a result, recent data from the T1D Exchange shows that in the U.S., only 34 percent of adults and 22 percent of children and adolescents meet the recommended A1c target of less than 7 percent. Put another way, 66 percent of adults and 78 percent of children and adolescents are not able to meet their treatment goals.

In the U.S., there is a 13-year difference in life expectancy for those with type 1 diabetes compared to those without. Globally, this gap is

approximately 24 years and as high as 46 years in low-income countries. This is simply unacceptable, and until there are cures, new therapies that give people with T1D more options to best manage their disease are sorely needed. The availability of once-weekly insulin will help meet the needs of people living with T1D in many ways.

As has been discussed today, a higher rate of hypoglycemia was seen in the ONWARDS 6 trial, most notably with self-measured blood glucose, SMBG. The comparator was daily administration of the second generation basal analog degludec, which has a significantly lower rate of hypoglycemia than insulin glargine, which is the basal analog with daily administration most frequently used in the U.S.

It is important to note that this risk in ONWARDS 6 is also observed to decrease meaningfully when assessed with continuous glucose monitoring, CGM, data. The median CGM-based hypoglycemia duration was also found to be comparable between the treatment arms. JDRF supports the use of CGM

for all people with T1D, as this gives a better picture of glucose levels than SMBG and provides better information for individuals to manage the risk of hypoglycemia that accompanies the use of insulin products.

Nearly 40 percent of people with T1D miss at least one basal insulin dose per month. Reducing the number of injections required means more convenience, better adherence, less burden, less risk for injection site reactions, and less potential for dosing errors. Recent international real-world data from 3,945 adults with CGM coverage and SMART [ph] pending data has shown that missing two basal insulin doses over a 14-day period would be associated with a more than 5 percent decrease in percentage of time-in-target glycemic range, 7280, which is considered clinically relevant.

Missed doses may also lead to diabetic ketoacidosis, or DKA, a serious metabolic condition with mortality rates as high as 4 to 10 percent. DKA commonly results from insufficient insulin administration, and once-weekly insulins will

likely mitigate this risk by maintaining the presence of insulin and minimizing missed doses.

If determined by the FDA to be safe and effective, the addition of the first once-weekly insulin will help to address the stark unmet needs of those living with T1D. Our hope is that as we gain more experience with this type of therapy, the entire T1D population will be able to benefit. On behalf of JDRF, I would like to thank the committee, FDA, and the sponsor for their careful consideration of the benefits and risks of this important new option for people with T1D. Thank you very much.

DR. LOW WANG: Thank you.

Now, we'll move on to speaker number 4. Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 please begin and introduce yourself? Remember to state your name and any organization you are representing for the record. You have five minutes.

MS. CLOSE: Hello. I'm Kelly Close, founder of Close Concerns. We have no financial

disclosures. As background, my team at Close Concerns and I live to make people smarter about diabetes through a new service, Closer Look, that we created back in 2005 that focuses on dozens of scientific, regulatory, and advocacy meetings that we attend each year. Today is one of those meetings, and we couldn't be more grateful to be here.

First of all, for everybody without diabetes -- I mean, if you took long-acting insulin, would you rather take long-acting insulin once a day or once a week? Risk mitigation has come so far, and we salute an unsung hero today. CGM clearly has made what is happening in diabetes so much more understandable. We've seen it. We've seen it all morning, and we love that everyone here can understand diabetes better because of this technology, and this technology can make a huge difference in a weekly.

So we believe recommending approval of once weekly could reduce burden for some people with diabetes. It isn't everyone, but it could be so

many, and especially many who have been marginalized, who don't have nearly the care that they need, maybe who have had to survive on not even just NBI, but taking NPR, and taking NPH, and R insulin rather. Many of those people, they could leap frog not just going to long-acting insulin and not just going to next-gen long-acting insulin, but going to once-weekly insulin. You guys have an amazing chance to make this happen.

Many people with type 1 diabetes and type 2 diabetes are already on automated insulin delivery, which is ADA standard of care for those on prandial insulin. Of course, given the heterogeneity of diabetes, it's not right for absolutely everyone, and not one of us with diabetes is doing well, but everyone is doing well, and this is possible. Once-weekly insulin could meaningfully improve adherence for those who need it and could improve not just their glycemic health, but also their heart health, their kidney health, their liver health. Complication reduction has never been so possible, and thank you to FDA for your work for

this end. Once-weekly insulin has a key place here, and so many of the interventions that you have made possible over the last 10-15 years have made a huge difference here.

Amid the ADA's very impressive drive towards standardization in the care of people with type 1 diabetes and type 2 diabetes, treatment still should be personalized, and maybe it should be especially personalized now. And for those clinicians who recommend once weekly to their patients, if we're lucky enough to see approval today, we stress and plead to you that it absolutely must be used alongside CGM, and thank you in advance to the panelists today for prioritizing this. If somebody says that they don't want to or can't afford to use CGM, then we hope that we'll work to get them CGM so that they can use this innovation of once-weekly insulin.

Well, hypoglycemia is an important concern. Hypoglycemia is preventable with continuous glucose monitoring, standard of care, again, for all people on insulin, and it routinely reduces the number of

hypoglycemic events in people with T1D and for many with T2D, again, those on prandial insulin, and for those with problematic hypo who are on sulfonylureas, many of whom, by the way, could undoubtedly benefit from once-weekly insulin; CGM is right for them, too, so thank you to FDA.

CDC reports that severe hypo numbers are going down. 240,000 people visited the ER in 2016 for severe hypoglycemia. That number was down in 2022 to 200,000. That is because of all of you, so many of the stakeholders here. Type 1 diabetes is a 24/7 responsibility, as you've heard from panelists today already. Managing this disease looks different for every one of us. What I believe we can all agree on is that we would appreciate additional options and choices for managing diabetes and opportunities to reduce the amount of time we need to spend each day managing it.

We recognize that the FDA advisory committee's role is to assess clinical benefit versus risk. There is risk here, no question. It

can be mitigated. Certainly, given ADA's standard of care, automatic insulin delivery is the first choice for most people with type 1 diabetes and type 2 diabetes using prandial insulin if they can afford it, but not everybody can wear or afford an automated insulin delivery device, and for these folks, we hope they can get a weekly.

Elaine Young, my colleague at Close Concerns, and multiple other team members also wanted me to convey their hope that FDA will recognize and consider the diverse perspectives and experiences held by over a million and a half adults in the U.S. with T1D, including people who struggle to take insulin on a daily basis, people who are hospitalized, people who live in nursing homes like Julie said, rehab centers, and more. While a weekly will not be absolutely straightforward management for those going into or coming out of the hospital, not even close, there's going to need to be a lot of work, a lot of advisory boards, but we believe the chance for people to have another option in the treatment

armamentarium for type 1 diabetes is invaluable.

In closing, you've done so much for us people with diabetes, over so many years. A lot of the innovation over that time has been for people with type 2 diabetes, primarily, more so than type 1 diabetes, and a lot of the innovation has been for those who have resources. Today is for those in the shadows. While it goes without saying that people with type 2 diabetes can benefit from once-weekly insulin, you also can meaningfully improve life for people with diabetes for everyone, especially if you make sure that they have the invaluable tool of CGM. Banting and Best I think would be so happy to see this approval. Thank you very much.

DR. LOW WANG: Thank you.

Speaker number 5, please unmute and turn on your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

MR. BELTRAN: Good afternoon. My name is

Alan Beltran, and I'm a research analyst at dQ&A. With me are Andrew Goyette and Mahima Chillakanti, associates at Close Concerns. dQ&A is a healthcare market research company focused on diabetes with several companies in the industry as clients. Close Concerns operates an independent information service focused on diabetes, pre-diabetes, and obesity.

The data we are about to present comes from a dQ&A national survey of over 6,000 patients with type 1 and type 2. This data was collected over several weeks earlier this month. Neither of our two organizations have received funding from Novo Nordisk for this research, nor have we consulted with company about these results.

Eligible survey respondents were shown this question. They were told that a major insulin manufacturer is currently developing a once-weekly basal insulin that would be as safe and effective as other daily basal insulins currently available. They were also explicitly told that hypoglycemia is the most common side effect, especially for

type 1's who are at higher risk than when taking daily basal insulins. In total, 1,876 patients answered this question.

MS. CHILLAKANTI: So looking to sentiment among people with type 1 diabetes, out of a strong sample size of 438 people on multiple daily injections of insulin, 1 in 4 said that they would definitely use a weekly basal insulin and 44 percent said that they would likely use a weekly basal insulin; 26 percent said they would likely not use weekly insulin and 5 percent said that they would definitely not use weekly insulin. Note that 82 percent of respondents use CGM.

Fewer injections and convenience were the biggest reasons for positive sentiment. Ten percent of positive verbatims also indicated a desire for better diabetes management. Meanwhile, out of those expressing negative sentiment, nearly half raised concerns about hypoglycemia, driven in part by the mention of hypoglycemia in our survey question. Overall, nearly 70 percent of respondents, or 302 people, indicated that they

would either definitely or likely use a weekly basal insulin, which leads us to believe that once-weekly insulin could be a valuable option for some patients who may even prefer it over once-daily insulin. As is with glucose lowering therapies, hypoglycemia risk medication remains critical.

MR. GOYETTE: While we realize that this meeting focuses on type 1 diabetes, we do see similarly high positivity among people with type 2, where use of this insulin may be less controversial, and that sentiment comes from very similar reasons as those mentioned by people with type 1 diabetes. For those on basal bolus insulin, fewer injections and convenience were also mentioned frequently as positives. In contrast to those with type 1, hypoglycemia concerns were not common.

Among those on basal-only insulin, we also see that reduced injection burden is mentioned frequently as a positive, and again, we did not see significant hypoglycemia concerns. Those not on

insulin who have discussed starting it with their healthcare provider also expressed similar positivity to other groups. Since hypoglycemic concerns may be greater among those with type 1 than type 2, education and discussion of risk management between people with type 1 and their care providers are clearly needed if this insulin is made available.

MR. BELTRAN: To summarize, these results show considerable enthusiasm for a once-weekly basal insulin among type 1's and especially among type 2's, but they also underscore a need for proper patient education and for risk mitigation in all its forms. Among type 1's expressing negative sentiment, hypoglycemia was by far the biggest concern compared to type 2's expressing negative sentiments who were primarily concerned with not wanting to change their current therapy regimen. Respondents with negative sentiment were in the minority, but there are actual insights to be taken from their hesitation about the implementation of this product and the risk management that providers

and patients would need to take. Thank you very much for your time today.

DR. LOW WANG: Thank you.

Now, I'd like to move on to open public hearing speaker number 6. I understand we have three speakers for this slot as well, for this five-minute time slot. Speaker number 6A, please unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? And for each speaker, please remember to state your name and any organization you're representing for the record. You have a total of five minutes. Thank you.

DR. REDDY: Dr. Low Wang, 6C is the first speaker.

DR. LOW WANG: Okay, go ahead. Thanks.

DR. REDDY: My name is Sethu Reddy, Past President of the American Association of Clinical Endocrinology, and we represent AACE today. I'll start off, and then hand over to Professor McGill, and then Dr. Biggs.

My previous roles have been as Chair of

Endocrinology and Diabetes Metabolism at -- is my microphone on?

DR. LOW WANG: I can hear you fine.

DR. REDDY: -- Cleveland Clinic and as Chief of Adult Diabetes at Joslin Diabetes Center. Thank you for this opportunity. It was very helpful to hear both the sponsor's and the FDA analysis; two observations before I hand it over to Dr. McGill.

Clinical research protocols tend to be very rigid and often hinder the clinician to provide optimal individual care. If one strays from the protocol, the study gets sabotaged and is for naught, so it is not the same as the real world taking care of patients.

The other point, without reiterating the care gaps and the needs for those with type 1 and type 2 diabetes, let me highlight one observation over the last 40 years, beginning with beef/pork insulin, and lente, to NPH insulin, all of which were highly variable pharmacokinetics from day to day. I realized that as a practitioner, the most important facet of insulin is its reproducible

and predictive kinetics. This allows me to tailor the regimen according to how an individual patient responds to the particular insulin type and dose, so going from population statistics to individual care is quite a different matter.

I'll now ask Dr. McGill to say a few words.

Dr. McGill?

DR. McGILL: Can everybody hear me? I was not able to hear --

DR. LOW WANG: Yes.

DR. McGILL: -- Dr. Reddy. Can you hear me?

DR. LOW WANG: Yes, I can hear you.

DR. McGILL: Okay. I can't hear others.

So I'm Dr. Janet McGill. I'm Professor of Medicine at Washington University School of Medicine, and I, too, represent AACE and practicing endocrinologists and physicians who treat diabetes. We, to reiterate, have reviewed the safety and efficacy data. We also want to speak to the care gaps of current insulin therapy.

We must treat patients who are not enrolled in clinical trials, who've had DKA for 3 or 4 times

this year, who have an A1c of 13. We have to design clinical and effective regimens for patients who struggle to take insulins or patients who require caretakers of one sort or another. We support the approval of insulin icodec for all insulin-taking patients. Thank you.

DR. BIGGS: Hi. Can you hear me ok?

DR. LOW WANG: Yes, I can hear you.

DR. BIGGS: Okay, good.

My name is William Biggs. I'm an endocrinologist in Amarillo, Texas, and I'm the CEO of an accountable care organization that oversees care for about 35,000 people in the Texas panhandle. I've been an investigator in the ONWARDS trials. I've got three perspectives that I'd like to share.

First, as an ACO director, we have a large cohort of patients with special needs that would greatly benefit from a once-a-week insulin schedule. For instance, we have home health agencies visiting patients for the sole purpose of of giving daily insulin injections in their homes.

We foresee an environment where we'd be able to do more remote patient monitoring and have home agencies visit them weekly instead of daily, resulting in lower costs and still providing the same degree of supervision.

As an investigator, one of my concerns was the transition of care for patients to hospital or surgical settings, if that became necessary. I did have the experience of two of our patients that were hospitalized during the trials, and we communicated with the hospital staff and surgeons that they were on an investigational, long-acting, weekly insulin and that we needed additional monitoring to ensure their safety; and it was to our pleasant surprise that the glycemic control was actually superior to what we usually saw with dose transitions.

The transition into the hospital often entails quite a delay in the ER, where the patient's diabetes is not dealt with necessarily appropriately or in a timely fashion, and the long duration of action of insulin was actually a

benefit. We didn't encounter any hypoglycemia and the post-operative courses were actually smoother than we expected.

Finally, as an investigator, I have to say that this insulin was somewhat unique in that our patients really didn't want to go off of the icodec at the end of the trial, that they were asking for extensions that we did not have the ability to give them. Most of our patients indicated that they would like the option to extend their time on weekly insulin and almost begrudgingly accepted going back to daily insulin. So this does indicate that there's an unperceived and unmet need for a weekly insulin, and all three of us are available for questions if you have any from the committee. Thank you.

Clarifying Questions (continued)

DR. LOW WANG: Thank you all so much.

I think that now we are at the end of our open public hearing portion of the meeting, and we will not be taking further comments from the audience. I would like to express my sincere

thanks to all of our OPH speakers for sharing your experiences, your thoughts, your insights, and opinions regarding today's topic.

We do have some additional time, and I'd like to take remaining clarifying questions. Again, please use the raise-hand icon to indicate that you have a question, and remember to put your hand down after you've asked your question. Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible. And as a gentle reminder, it'd be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That's all for my questions," so we can move on to the next panel member.

So I do see that Dr. Crandall has her hand up, so I'd like to call on Dr. Crandall.

DR. CRANDALL: Thank you. Jill Crandall. This is, I think, a question for the sponsor. It was mentioned earlier about the specific language

in the EMA approval for insulin icodec, something to the effect of for type 1 diabetes, it was indicated special populations are only of clear benefit, so I could use more information about that language.

DR. LOW WANG: Could I ask Novo Nordisk to go ahead and respond to that question?

DR. GOUGH: Yes. To take that question regarding the EMA indication or approval, I'll hand over to my executive director in Regulatory Affairs, Shawn Hoskin.

MR. HOSKIN: Shawn Hoskin. The indication is for treatment of diabetes mellitus in adults, and it's for patients with both type 1 and type 2 diabetes. There were a number of different risk mitigations which were proposed in the EU label. The first was that for type 1 patients treated with insulin icodec, that there was a higher risk of hypoglycemia compared to insulin degludec. Patients with type 1 diabetes should only be treated with insulin icodec if a clear benefit from a once-weekly pathology is expected, and that most

hypoglycemic episodes were observed on days 2 to 4 after the weekly administration.

Previously, I believe there was also a question regarding the EU label regarding whether newly diagnosed patients should be included or not, and there is information in the EU label in the Special Warnings and Precautions section, and there it is noted that the safety and efficacy of icodec in newly diagnosed type 1 diabetes patients have not been established and that no data is available yet. So that was the information related to newly dosed patients that was included in the EU label.

DR. CRANDALL: Thank you.

DR. LOW WANG: I'll ask just a follow-up question related to the EU label. Could the sponsor please clarify whether or not this has been approved in the EU yet?

DR. GOUGH: Yes, I can confirm it has been approved in the EU. Maybe I could also ask, Dr. Wang, at some point, we'd be grateful if we could add some further information. There were a few questions before lunch that I think required

some further data and further response, and when you think it's appropriate, we would be delighted to do that.

DR. LOW WANG: Yes, thank you. We'll see how the time goes.

So let's move on to Mr. Tibbits.

MR. TIBBITS: Thank you. Paul Tibbits. This is a question for Novo Nordisk. One of the things I discussed earlier -- and I think it was implicit and potentially one of Dr. Low Wang's questions -- is how patients, particularly type 1 patients, self-managed with their boluses during the course of the week.

Did you collect data, either through a patient diary or any kind of way, about what a patient's weekly or daily bolus amount was in a way that we could separate it from a day-to-day basis and day 1, day 2, day 7 to see what those fluctuations might look like?

DR. GOUGH: Yes. I can confirm, we did collect that information. We collected information on a bolus dose and bolus dose adjustments on days

of the week. And what I can show is in ONWARDS 6 -- and what I'm showing on this slide is ONWARDS 6 -- I'm showing you the daily total bolus insulin dose on the Y-axis and the days of the week on the X-axis, and in gray, you can see insulin degludec and in blue you can see insulin icodec.

You can see that in the trial, there was a small reduction by patients on days 2, 3, and 4, and this was not of the order of magnitude that we would anticipate would be required to impact on the rate of hypoglycemia, but certainly some patients did make that dose adjustment. So I hope that provides you with the information that you've requested.

MR. TIBBITS: Sorry. If I could just jump in, Dr. Low Wang, it does to some degree, but just to make sure I'm reading the material correctly, this is essentially a mean across all patients reflecting the last 2 weeks of the planned treatment, right?

DR. GOUGH: That is correct, yes.

MR. TIBBITS: Okay. Perfect. Thank you.

DR. LOW WANG: Thank you.

Before we move on to Dr. Greevy, I just wanted to see if Dr. Onumah had a question. You had a raised hand before our break, so I just wanted to confirm.

DR. ONUMAH: I did, but that question actually was a comment, and it was actually explained by several other members. It was concerning the CGM and the blood glucose monitoring, and where the data might be a little different.

DR. LOW WANG: Okay. Alright. Terrific.

Then moving on to Dr. Greevy.

DR. GREEVY: This is Robert Greevy. One comment that's come up in every set of sessions, the public session, the FDA's presentation, and the sponsor session, is that degludec is really a platinum standard for hypoglycemia to compare against; it's just exceptionally good at not causing hypoglycemia.

Is there a way to quantify that for us? I've been just digging around. I'm getting a sense

that glargine, for example, in comparison to degludec, seems to have a relative risk of around 1.6 or so, and I'm just looking to see if anyone has better quantification than that for me.

DR. GOUGH: So you're correct. We did choose degludec, if you like, the platinum standard in terms of its rates of hypoglycemia. Indeed, degludec is the only basal insulin that has within its label reference to the fact that there are lower rates of severe hypoglycemia with insulin degludec compared to a basal insulin comparison, so we did go up against a very strong basal insulin in ONWARDS 6.

It's always difficult to do indirect comparisons between trials because there are so many things that are different, but if you look at previous trials where event rates have been somewhere between 25 and 40, level 2 and level 3 event rates per year, we know that in our trial, those events rates were about 50 percent of that, about half as much. And I think that's important to contextualize, to put it into absolute terms.

We have been talking about the relative risk between two insulins, insulin icodec and degludec, but if you look at the absolute rates of hypoglycemia, you're quite right; these are low in ONWARDS 6.

DR. GREEVY: Thank you.

DR. LOW WANG: I would like to find out whether or not the FDA would like to respond to that question as well.

DR. ARCHDEACON: Thank you, Dr. Low Wang. This is Patrick Archdeacon. I think we would mostly emphasize the challenges with doing cross-study comparisons, so I think we're mostly focused on the trial data that we actually have in front of us.

DR. LOW WANG: Okay. Thank you.

Next, Dr. Beringer?

DR. BERINGER: Yes. Paul Beringer. I just have a clarifying question about the risk mitigation strategies that were proposed. The analysis showed what effect each of these individually would have, but it appears that it is

proposing that all these be used, or are they supposed to be determined on a patient level, one strategy versus another? What's actually being proposed?

DR. GOUGH: I think what's important here is individualization of care that my clinical experts have previously talked about. When we look at patients with type 1 diabetes on basal bolus, there are many things that a healthcare professional and the patient can do to improve glycemic control and reduce the risk of hypoglycemia. So in terms of our mitigation strategies, this is a collection of activities that most -- in fact, all -- healthcare professionals managing type 1 diabetes are familiar with, is the appropriate selection of patients, and certainly with insulin icodec, we would not recommend this for patients with hypoglycemic unawareness or severe recurrent hypoglycemia.

We would like to communicate the increased risk of hypoglycemia on days 2 to 4 after a weekly injection in some people, so those patients who are experiencing difficulties with hypoglycemia,

they're aware that on these days that's likely to be the greatest time that they'll have the problem, and that's when they may well want to choose to make a a reduction in the bolus dose, whether it's an order of magnitude of 30 percent or whatever.

I think all of these things -- reassessing thresholds, whether the insulin regimen is right, whether it's the right insulin -- there are so many things that a healthcare professional considers on a regular basis, and we're advocating that this should be part of that. And maybe to add some further insights on that, I could call upon my clinical expert just to place what we're saying into context.

DR. LINGVAY: Well, thank you. Ilda Lingvay. I appreciate your question because these models are done at a study level and do not really apply to the individual patient in the study, especially in the setting of type 1 diabetes. The customization of therapy to the individual, it's true for every patient. Every patient is different in type 1 diabetes. Every patient with type 1

diabetes is different, and we really have a custom plan for every patient. So that's why when a study level adjustment is recommended, it's meant to work for some people, for the average person, but not for the individual person.

So to answer your question, based on the ONWARDS 6 study, what I foresee happening in clinical practice, the majority of patients will probably not need any adjustments. They did well in the study, they had target time below range, they had target time in range. Probably more than half of the patients will not need any adjustments.

Those other ones who are at higher risk of hypo or turn out that they start on this medication and they start having some more hypos than they had before, the individualization of therapy is going to occur, and it's not going to be one prescribed individualization or the other; it's going to be a trial and error of combination of interventions that we're already used to in clinical care.

We do this with every patient right now. The same treatment doesn't work the same way for

every patient with type 1 diabetes, so we already are accustomed to that, we're already doing that, and we will do that in the setting of icodec use as well. We will individualize the treatment. We will apply a reduction in bolus if that's appropriate for the patient or some other mitigation strategy that we think is best for that one individual.

DR. BERINGER: Great. Thank you.

DR. LOW WANG: Great. Thank you.

Dr. Brittain?

DR. BRITTAIN: Yes. Thank you. So I wanted to go back a little bit to the question about the subgroup with the coefficient of variation less than 36. I know Dr. Nason asked some questions early on about it not being a baseline determined subgroup and the FDA made some comments along those lines.

I'm not totally sure what your final answer to Dr. Nason was. Are you able to use any baseline, true baseline, data to determine those subgroups?

DR. GOUGH: Yes. Thank you, and I appreciate that this question was asked this morning, and I do have some further information that I'd like to add in this regard.

So as you say, there was concern expressed about the use of post-baseline coefficient variation or glycemic variability data as compared to true baseline pretreatment values. We showed the phase 1 study, which demonstrated that the mean glycemic variation was stable pre- and post-treatment, but you appropriately asked about individual participant data.

If I can just put the next slide up, what you can see is this slide shows individual participant data from the same study. The Y-axis shows glycemic variation during the insulin glargine treatment period and the Y-axis [sic] shows glycemic variation during the first 14 days of the subsequent insulin icodec treatment period, with the line of unity also shown. And as you can see, there's a strong correlation in the continuous glucose monitoring glycemic variability between pre

and during treatment with insulin icodec. So we're confident that the glycemic variability data from week 0 to 2 from ONWARDS 6 largely represents patients' baseline glycemic variability.

DR. BRITTAIN: Okay. But apparently you don't have data on everybody, just a small subset.

DR. GOUGH: Well, this isn't a subset of the phase 3 study; this is a specific study, phase 1.

DR. BRITTAIN: Oh, I'm sorry. I'm sorry. Okay. Thank you.

DR. GOUGH: Thank you.

DR. LOW WANG: Okay. Terrific.

So if there are no more clarifying questions from the panel, we'll take a short break. But to make sure that we have enough time for our discussion and voting, I'd like to reconvene in 10 minutes. So that would be at 2:22, so we'll see you back in 10 minutes.

(Whereupon, at 2:12 p.m., a recess was taken, and meeting resumed at 2:22 p.m.)

Questions to the Committee and Discussion

DR. LOW WANG: Welcome back.

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. We will now proceed with the questions to the committee and the panel discussions, and I'd like 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.

Let me give you an outline of our schedule. It's about 2:23 right now, and we have four discussion questions before the one voting question. So we'll have approximately a little over an hour for the discussion questions. So no later than approximately 3:30 or 3:35, we'll take the time necessary for the voting question and the vote, and ask every voting member of the panel to explain their vote. If this plan meets with your approval, I'll read the first question. After I read the question, we'll pause for any questions or comments concerning the wording of the question.

We'll proceed with our first question, which is a discussion question for the panel. The question is, discuss the benefits of insulin icodec and the risk of hypoglycemia in adults with type 1 diabetes mellitus.

Are there any questions about the wording of this first discussion question? Go ahead. Dr. Greevy

DR. GREEVY: This is Robert Greevy. I just wanted to ask if we needed to tease out benefits, if that needed to be more clearly defined into how broad that term should be.

DR. LOW WANG: I'll let the FDA respond to that, but I think in terms of my thoughts on this, I think this is how you see the benefits, or potential benefits, for insulin icodec, and we'll be addressing various aspects of risk versus benefit profile through the course of our discussion and the voting question. But FDA, would you like to expand further?

DR. ARCHDEACON: Hi. This is Patrick Archdeacon. No, we'd endorse that position,

Dr. Low Wang. I think at this point, we're interested in the opinions and the perspectives of the panel members.

DR. GREEVY: Thank you.

DR. LOW WANG: Thanks.

Dr. Brittain?

DR. BRITTAIN: Maybe it's the same question. I guess when I read this, I don't know if it's about the benefits that are seen in the data set or just any theoretical benefits.

DR. LOW WANG: I do think all of that may come up during our discussion, so I think we'll -- does that help? Okay.

DR. BRITTAIN: That's fine.

DR. LOW WANG: Awesome. Great. So then in that case, maybe we should go ahead and start. Who would like to start?

Mr. Tibbits, go ahead.

MR. TIBBITS: Sorry for the change in appearance. I'm getting a little cold, so I put a sweatshirt on. Sorry. Paul Tibbits.

Maybe I'm not the right one to start, but

I'll start anyway. I think as a person with diabetes or people with diabetes, what we're really looking for, as I think one of the public presenters noted -- there's potentially 42 different aspects of daily life that might impact your blood sugar, so one of the things, certainly, that I'm looking for and probably a lot of us are looking for is consistency on a daily basis.

There are certainly going to be factors in life that we can't control, so to the extent that we can't control them, I think so much the better. I think, overall, there seems to be a strong argument that there are benefits for insulin icodec -- and again, just in type 1; I'm not talking about type 2, that there are certain benefits for what I would argue is potentially a small group of the type 1 community for whatever reason, whether they're in certain care settings, or they have a fear of needles, and what have you.

On the other hand, I'm not convinced that this is providing any sort of daily regularity, which to some degree it seems like the applicant is

suggesting that it does. I would argue that in certain days, it might actually be introducing additional variables that would need to be included in a patient's life, which would make it potentially harder in terms of a day-to-day calculation and day-to-day consistency and regularity.

So I don't know, to me at least, that the benefits so clearly outweigh the risks, certainly for the broad population. I think if we start thinking about label constriction, label restriction, and who this might be applicable for, then my position might change, but very broadly, I think right now it does seem to be -- at least in my mind, there is some amount of risk that I think we need to account for as we think about who this might ultimately benefit.

DR. LOW WANG: Thank you for those comments.

Dr. Onumah?

DR. ONUMAH: I think that we've seen both sides of the discussion in terms of benefits and risks, but I'm going to be commenting as a

clinician in practice and always looking at my job as a clinician in terms of finding the right tool for each individual patient that I see. In this instance, when I think of benefits for insulin icodec, I think that it will not be beneficial for every person, but it might be useful for some persons.

Certainly, in my mind, there are still a few risk mitigation things that need to be ironed out clearly so that for the general provider or practitioner who would be writing this prescription, should it be approved, we will be doing it correctly and safely because safety would be very important. But I think it would offer benefits. It would be a tool that would be helpful to be added to the toolbox for the clinician to be able to reach for, for the right person.

DR. LOW WANG: Perfect. Thank you.

Dr. Kalyani?

DR. KALYANI: Thanks. Rita Kalyani. When I approach benefits, I think there are theoretical benefits. So clearly having a new treatment

modality, which would be once-weekly insulin, offers a theoretical benefit of reducing treatment burden, simplification of regimens perhaps for those who have a fear of injections, facilitating them to take insulin. So there are definitely many theoretical benefits.

When we look at the benefits that were demonstrated in ONWARDS 6, I think we do see that some of them have held true. We see the A1c lowering efficacy. We see that, while the satisfaction survey had its limitations, overall there was in both arms a favorable signal.

I do think that the question of general benefit versus targeted benefit for some populations will help guide our discussion because it could help guide the responsible use of this medication, which is what I think we're all talking about here today, and that gets to the risk of hypoglycemia, which was clearly demonstrated and we know is a risk for any insulin that we currently have available. I think the question is whether the hypoglycemia can be prevented and identified

early with the monitoring strategies we have, such as CGM.

I do think it's important to note that in ONWARDS 6, it was not part of the titration schedule and that people titrated on a daily or a every few daily basis like we would in clinical care; instead it was more a weekly schedule, so perhaps more frequent titration may mitigate that hypoglycemia. But I do think that the risk of hypoglycemia is real in some populations and that thinking about the benefit to risk, it's important for us to think about which populations could benefit from this more.

But at the end of the day, the question is also, who decides that for the person with diabetes? Is it the preference of the person with diabetes who then decides whether this insulin would facilitate their day-to-day care? And then as a clinician, as was mentioned, too, having more tools that we can personalize for people with diabetes also broadens our ability to really meet the outcomes for people with diabetes. So that's

just some of my thinking.

DR. LOW WANG: Thank you.

Dr. Brittain?

DR. BRITTAIN: So again, I agree that there are theoretical benefits and anyone could understand wanting to have fewer injections, and that's very important. But, unfortunately, within the trial data, we don't see the benefit of better glycemic control, which I think was promised in terms of adherence. I understand that that would be hard to show in this clinical trial population, but things kind of go the other way.

Likewise, for the treatment satisfaction survey, even though it has its own issues, I'm a little disappointed that given we heard all the anecdotal data that people who were in the trial, who were on the once-weekly treatment, really were sad to not be able to continue with that, I'm sort of surprised that that wasn't borne out in that data, as flawed as it might be, the survey data.

I guess the other comment I have is there was some talk that I heard from a number of people

that there are different populations that probably would benefit most from this, but they weren't really the populations studied in this trial, and I do wonder if there would be different concerns about hypoglycemia management in these different populations. That's it.

DR. LOW WANG: Thank you.

Dr. Crandall?

DR. CRANDALL: Yes. I think this is really -- I guess always but especially here -- a risk-benefit analysis. We clearly know the risks. They've identified the risks pretty well for us in terms of the hypoglycemia. I think the benefits are largely theoretical, and I'll just state the obvious. Type 1 diabetes has huge treatment burden, and any of us affected by diabetes or treating people with diabetes know that. But in my assessment of the situation, the biggest burden is not related to the single daily injection of basal insulin, it's to the bolus insulin and all the calculations and concerns about matching to carbohydrates, et cetera, that patients have to go

through.

So the real benefit in terms of reducing treatment burden would be from just removing this one injection a day? I don't know. I've been dubious about that, despite the fact that we've had some testimonials from the public and reported from the trial that seemed to suggest that this is meaningful to people. That's a question mark to me because I think if there isn't a reduction in treatment burden, then I'm not sure that the risk of hypoglycemia is worth it.

I think probably zooming in on or trying to identify the population or what segment of the population with type 1 diabetes might benefit from it, I think it would be very useful, but we don't have very much to go on from the trial data that they provided us because of the very restricted nature of the people who enrolled in a clinical trial; for example, a population that's been frequently cited as patients with very poor medication taking habits who frequently end up in the hospital in DKA because of lack of insulin.

That's attractive to think that this might be helpful for them, but we're not really sure about that, and in many cases, these are the same people who wouldn't be using a CGM or may be doing or having other risky behavior that would actually make it more risky for them to be using this insulin. So I think there are a lot of questions in my mind about the benefit end of this, whereas the risk I think has been pretty well spelled out.

DR. LOW WANG: Thank you for those comments.

Mr. Tibbits?

MR. TIBBITS: Thank you. Paul Tibbits. I think the other piece of it, and I think it touches a lot on Dr. Crandall's comments, is how does this translate into the real world? I know this is probably a question you all wrestle with as committee members with all clinical trials, but for me as a person with diabetes, I think about, as somebody said, degludec is the platinum standard for long-acting insulin, for basal insulin.

I assume that a lot of you folks are the platinum standards for endocrinologists, so when

you think about your run-of-the-mill endocrinologists, or even patients that don't see endocrinologists, they see general practitioners, what is the ability for the patients who this is intended for to actually work on a day-to-day, week-to-week basis with their healthcare professional? Because in a clinical trial, certainly you can work with your clinical team on a day-to-day, week-to-week basis, but I don't know that that reality is borne out for most people with type 1 diabetes.

So I think I do still have a lot of open questions about the risk mitigation strategies. Do we live in a world, once you apply the real-world restrictions, including insurance and whatnot, do we actually live in a world where these risk mitigation strategies are readily available to the people who would be receiving this insulin?

DR. LOW WANG: Yes. Thank you for those comments, and I would agree that I think that's always a question that we struggle with, is how do we translate these clinical trial data to the real

world? My experience is that oftentimes patients who have recurrent DKA because of lack of insulin also tend to be patients who are over basaled [ph], have higher doses of basal insulin in order to reduce numbers of injections of bolus insulin, which may place them at higher risk for hypoglycemia.

So I'd like to make a few comments before we move on to the raised hands. As member and chair of the panel, I really appreciate the comments made by the committee so far, and in considering this question, the main potential benefit is the lower number of insulin injections, reduced burden of treatment, improved satisfaction, improved adherence. And the only factor of those that's really been demonstrated to be improved with insulin icodec is the number of insulin injections.

So I'm concerned about the increased risk for hypoglycemia that was seen in ONWARDS 6 for patients with type 1, not just in the incidence and rate of the hypoglycemia, but also the higher number of serious adverse events due to

hypoglycemia associated with loss of consciousness and causing people to need to be hospitalized, emergency room visits, and all of those are anticipated to impact quality of life negatively.

Now, Dr. Kalyani?

DR. KALYANI: Thanks. I just wanted to add, in regards to the benefits, the variability that we saw with the pharmacodynamics, I don't know that that's an added benefit necessarily because the glucose variation we see already in people with type 1 diabetes, that variability of the medication itself now in terms of having a peak effect with days 2 to 4 and then wearing off later in the week, where we might actually see higher blood glucose, as we saw, when we look at those time in ranges, and there was not only more variability, but there's also more highs as well near the end of the week with the insulin icodec; that variability also introduces more uncertainty regarding glycemic control.

That being said, I do think that for some people for whom they, like we said, may be

reluctant to take injections daily, this could be an option to maybe even transition to the ideal or the gold standard that we've often talked about, which is the basal bolus regimen with the tighter control with the daily basal injection, and perhaps it could keep people who otherwise we see in the hospital out of ketoacidosis.

I do think that one of the things we should keep in mind is that in terms of approval, A1c lowering benefit has been the surrogate that we have used for diabetes medications to assess its ability to potentially produce long-term risk of complications, and I don't know that we are necessarily charged with saying that this is better than what we have currently out there, but is it sufficient as an option for people who would want to use it?

When I think of who might want to use it, for someone who's tightly managed, is at their A1c target, on a daily basal insulin with multiple bolus injections a day, I don't know that they'd want to switch to this necessarily. But perhaps

the person who's early in their disease, who may be reluctant to go straight to the 4 injections a day; those who have an unpredictable schedule; those who, for whatever reason, feel better about taking once-weekly injections instead of a daily injection; and those who are not at their targets -- maybe they're more like an A1c of 8 or 9, perhaps not over 10 because then I think we run the risk DKA -- perhaps they would be the ones that would benefit from this.

But I do think when we think of benefit, perhaps it doesn't need to be a comparative benefit, but more of an absolute benefit; is there a benefit for some people out there with type 1 diabetes to take this medication, and if so, should this be approved?

DR. LOW WANG: Thank you.

I'd like to wrap up this discussion question with Dr. Onumah's comments, so go ahead, Dr. Onumah.

DR. ONUMAH: Thank you. Barbara Onumah. I think Dr. Kalyani brought up some of the points

that I was going to raise, but to bring up a point that Dr. Crandall had mentioned before, I think we have some data, although not exactly the same, comparing once-daily injections to once weekly, and that's with the GLPs, and there's some data showing that there's increased adherence when we change from once-daily to once-weekly injections. So to that, in terms of benefit, if we could extrapolate that, we could say that there's potential that when we offer patients with diabetes once weekly versus once daily, there's a chance that it would increase the adherence, even though we don't know that for a fact, but we can extrapolate from that data.

Again, we've already discussed that this is not going to be for everybody, but for some patients, this might be the best option. In fact, we do that clinically when we actually have relaxed targets for persons who are a little bit difficult to control for various reasons, whether it's because they don't have access to medications or various reasons that affect the adherence, and we accept when they have not the ideal A1c but an A1c

that would be acceptable and get them not into trouble or get them to not have recurrent hospital admissions.

So the risk of hypoglycemia is real, and we have to have real factors to mitigate those risks, but the benefit would be for those persons having less injections and maybe making it a little bit more easier for them to take this option of insulin. Thank you.

DR. LOW WANG: Great. Thank you so much.

So I'd like to wrap up the discussion of this particular question, and we have a few more to go, so let me summarize our discussion. If you strongly disagree with my summary, please let me know.

So what I heard is that panel members commented on the importance of adding more tools to our toolbox for our patients. There's a hypothetical benefit of reducing treatment burden and improving medication adherence, but this is, of course, balanced with the risk of hypoglycemia and the ability of the proposed risk mitigation

strategies to reduce this risk, as well as introducing more variability due to the differences in pharmacokinetics over the course of the week.

There is a higher number of SAEs due to hypoglycemia leading to hospitalization or ER visits and associated with loss of consciousness with icodec, but another point was made that many patients are looking for consistency, so insulin icodec may provide benefits to a specific group of patients with type 1, but also introduces variables that might make it harder to have consistent glucose control on a day-to-day basis. So there are questions about, well, who decides this and who would benefit the most from insulin icodec, and how do we translate these clinical trial data to the real world?

Any comments that panel members would like to add?

(No response.)

DR. LOW WANG: If not, let's move on to question 2, which is also a discussion question. This is also a discussion question, our second out

of four. The question is to please discuss the role of continuous glucose monitoring devices and measures of glycemic variability with respect to the risk of hypoglycemia in patients with type 1 diabetes using insulin icodec.

First, are there any specific questions about the wording of this question?

(No response.)

DR. LOW WANG: If there are no questions about the wording, we'll open the question to discussion. And maybe as we're waiting for panel members to raise their hands, I'll start with a few comments.

We know that CGM has really revolutionized the care of diabetes and is recommended for all patients with type 1 by several professional societies. There are still problems with access for many patients, so this is still an issue that we need to deal with and resolve. We know that CGM also detects a lot more episodes of hypoglycemia than self-monitoring of blood glucose.

I think the data that was shown today

support the utility and probably the necessity of using CGM because of this increased risk of hypoglycemia that was noted in ONWARDS 6 with insulin icodec, and the analyses by both the applicant, as well as the FDA, do show that those patients with higher versus lower glycemic variability may have marked reduction in the number of episodes, as well as the rates of hypoglycemia on par with what was seen in the comparator arm with insulin degludec.

So even though we didn't have baseline coefficient of variability data for ONWARDS 6, the data that were shown seemed to demonstrate relative stability of the coefficient of variability over time that supports the idea that the post-baseline CV value might be similar to the baseline value. So I do think that the use of CGM and the use of baseline CV to try to risk stratify patients would go a long way toward mitigating the risk of hypoglycemia with insulin icodec, but what would happen with using an actual baseline CV value, we don't have those data.

Now I'd like to call on Dr. Nason.

DR. NASON: Thanks. Martha Nason again. I've been sort of struggling with the CV question because as I raised before, and as the FDA raised, and Dr. Brittain mentioned also, the fact that it isn't baseline data, it's not ideal, and it wasn't prespecified as well, but probably it does make some sense in terms of identifying who's at lowest risk for hypoglycemia.

It also doesn't necessarily mean that those are the people who can benefit most because even in that subgroup, even though it looked like they were at substantially lower risk of hypoglycemia than the people with a higher CV, there was still a relative risk of two that they would have -- I can't remember if it was based on one or more hypoglycemic episodes or the total rate, but it was still a fairly large relative increase in the rate of hypoglycemia among those who are taking the weekly dose compared to the daily.

So I think it certainly is important and it needs to be explored more, but I don't know that I

feel that we have the information yet about how to use that data, or even if baseline turns out to be the same as weeks 1 and 2, that that targeting necessarily means that those people are the ones who would benefit the most and that this is a good risk-benefit trade off for those people.

DR. LOW WANG: No, that's a really important point. Thanks for making that.

Dr. Kalyani?

DR. KALYANI: Thanks. Rita Kalyani. The role of continuous glucose monitoring, I agree that CGM, while widely recommended for people with type 1 diabetes, continues to be not equally accessible to all people with type 1 diabetes. So I think that access and coverage of CGM has to be taken into account, but clearly using CGM and having the availability of the functionality of trend arrows, of seeing patterns throughout the week, throughout the day, all of those things can help reassure the person with diabetes and their provider about safely using medications for diabetes, including insulin icodec given the PK

variability that we talked about. So I do think that CGM as an adjunctive treatment can be very helpful.

In regards to the risk of hypoglycemia in people with diabetes, type 1 diabetes, I think that the glycemic variability we talked about with the CV, I think it's important to think about absolute risk versus relative risk. And as Dr. Mason mentioned, even those with the percent CV that were at the lowest tier, they still had a higher relative risk compared to insulin degludec, but their absolute risk was lower. So I think we need to think about those two terms as well.

DR. LOW WANG: Thank you.

Dr. Greevy?

DR. GREEVY: This is Robert Greevy. There are two things I wanted to comment on that. The first, as was just mentioned, it does feel like there's some data that may be available that would be very helpful for us to know in that the data's pretty strong that the hypoglycemia risk relative to degludec is about 1.4 to 2 times greater, but

what I don't know is whether that in absolute sense is a high risk of hypoglycemia relative to people getting treated.

I mean, if degludec is just far and away the standard of care and it makes sense to use that as a comparison, then I'll take that as that relative risk is much more influential to me than if degludec is one of many treatments being commonly used and I need to think about comparison to the class as opposed to comparison to one particular drug.

So there is some information I feel like I'm lacking, specifically with regard to CGM. There may be information in the data, in the ONWARDS 6 trial, that could speak to the CGM risk because as was noted, it was important that this roughly doubling of the risk appeared in every subgroup analysis, so for any baseline risk that we construct, it appeared that icodec about doubled the risk.

The question remains, then, can CGM prevent hypoglycemic events? There may be information in

the data if we actually see people doing that because some of the people were on CGM and some weren't, and we know when they had their hypoglycemic events, and I should specify severe hypoglycemic events. So do we see that those who are on CGM are much less likely to have severe hypoglycemic events?

DR. LOW WANG: Thank you, Dr. Greevy. I do believe that all of the patients in ONWARDS 6 were undergoing CGM monitoring.

DR. GREEVY: Oh, okay. So it would only be if it was mixed in prior trials that we'd have to uncover it there.

DR. LOW WANG: Yes.

DR. GREEVY: Thank you.

DR. LOW WANG: But thank you for your comments; those are really important points.

Mr. Tibbits?

MR. TIBBITS: Yes. I think my read on the material that we saw was where we really saw the risk of hypoglycemia, where it seemed to be eliminated the most vis a vis degludec -- so not

eliminated totally but at least on par with degludec -- was the intersection of CGM and low glycemic variability. So I think as I'm thinking about this, I'm thinking about ways to make sure that this is getting to the people that need it but also not maybe getting to people who don't have the right constitution or the right access to be able to use it without danger.

I do want to go on the record to say that knowing that there are significant access issues to CGM, and then, potentially if this were to get approved, maybe significant access issues to this, if we were to say -- again, if FDA were to say we're going to restrict this to people that are on CGMs, then we're sort of doubling the access obstacles. So I think, morally, I feel a little concerned about saying, "Hey, there's an innovative treatment that people should have access to, but you might have access issues, and the only way to access it is to access this other mechanism which you're going to have access issues for."

So I do want to recognize that we may be

building access upon access obstacles if we go that route, but on the other hand, the data, at least to me, did seem to indicate that this intersection of CGM and low glycemic variability is really where we saw the most commonality or the most equality between severe hypoglycemia in the arms.

DR. LOW WANG: Thank you.

Dr. Onumah?

DR. ONUMAH: Hi. Barbara Onumah. I just have a quick comment in regards to the discussion question. I think it's pretty standard that we know that CGMs have revolutionized the way we manage persons with diabetes, and as it pertains to the question at hand, from the data we have just reviewed, the lower the glycemic variability, the lower the chance of having hypoglycemia. But in the data, it didn't really matter whether you had a CV less than 36 or not; it appeared that icodec was associated with more hypoglycemia compared to degludec. So I think that should be understood by persons who would be using this if this were approved, and we just need to have that

understanding.

So in regards to whether or not CGM should be used with this insulin, absolutely because it has revolutionized the management of diabetes, but in regards to whether or not glycemic variability affects hypoglycemia, the data suggests that even if you have a lower glycemic variability, it appears that you still have more hypoglycemia with icodec.

DR. LOW WANG: Great. Thank you.

Dr. Kalyani?

DR. KALYANI: Rita Kalyani. There were a few questions that came up about how clinically accessible is the percent CV. While it's one of the metrics that comes out on ambulatory glucose printout, I would say that it would be something that would be more difficult for someone in clinical practice, I would think, to have to constantly look at that number and then say, "Well, is this person really variable and not really variable?" Is this something that we would think about?

I would think about this more as a general concept, someone who has more variability versus less variability of the blood glucose, and if they don't have access to CGM, as we talked about, self-monitoring of plasma glucose was shown as an option. And for the motivated patient who can do the multiple finger sticks per day, I think that would be a great option.

I think the question is for the person who may not have access to CGM, who doesn't do the multiple monitoring with the self-monitor plasma glucose, is this still something that we would feel reassured we could mitigate the risk of hypoglycemia? I realize the question focuses specifically on CGM that we're asked to discuss, but I think it's important to keep in mind that if someone doesn't have a CGM, will they be self-monitoring; and if they're not self-monitoring, can they take this medication? And I think the answer would be no.

So there would have to be some kind of monitoring, but for those who don't have CGM for

whatever reason, could you do self-monitor plasma glucose, I think that would still be an option; but then we'd have to rethink how we're defining this variability, and perhaps it's by standard deviation like we talked about, which is something that we would be more likely to see in one of those printouts.

DR. LOW WANG: Great. Thank you.

Dr. Crandall?

DR. CRANDALL: Yes. I agree that there's certainly justification for requiring or expecting that anyone using this insulin would be also using continuous glucose monitoring -- I almost think that's sort of a no-brainer if there was access to it -- but I'm struggling, I think a little bit as Mr. Tibbits is doing, with trying to understand who the target population for this insulin would be, in that in many cases, the people with the greatest glycemic variability are people who are not monitoring regularly, who are not able to adhere to a complicated dosing schedule for their bolus insulins. And the people who have a lot of

glycemic variability and are not that consistent with taking their insulin are the ones who might benefit for long-acting insulin to prevent episodes of DKA and ending up in the hospital.

So I kind of go around in circles. The people who might benefit the most from the adherence aspect of once-weekly insulin are probably the people who may not be able to use it safely.

DR. LOW WANG: Thank you. Those are all important comments.

Are there any other comments from the panel on this discussion question?

(No response.)

DR. LOW WANG: So if there are no further questions or comments about this discussion question, I'd like to summarize. If you strongly disagree, please let me know. There were a number of issues discussed. I think what was mentioned is that although CGM is recommended for all patients with type 1 diabetes, access and coverage are still unresolved issues, and it does appear that to

mitigate the risk of hypoglycemia with insulin icodec, CGM is needed.

One thing I would like to point out is that in ONWARDS 6, all of the patients underwent continuous glucose monitoring through the duration of the trial and were asked to self-monitor 4 times a day. So what we're seeing in terms of the differences in risk of hypoglycemia, the rates of hypoglycemia were in the setting of CGM. So then, the question was raised, if this is the case, then, would this double the problems of lack of access in patients who need insulin icodec who may not be able to access this or CGM?

There were also problems expressed regarding the extrapolating recommendations and the risk mitigation strategies from the CV data. We don't have CV data at baseline. We also don't know if the patients with the lower CV are the same as those who would benefit the most from insulin icodec. And it was noted that there is a higher rate of hypoglycemia even in that lower CV subgroup as compared with degludec, and we're lacking

information about risk mitigation strategies and how effective they are.

Does anyone have any strong comments about this or would like to add anything?

(No response.)

DR. LOW WANG: Okay.

So then, let's move on to question 3, which is also a discussion question, so please bring up slide 4. Question 3 is also a discussion question, so I'll read the question and then see if there are any questions about the wording. Please discuss the proposed dosing and titration regimen and the extent to which the modeling data support alternative dosing strategies.

Are there any questions about the wording of this question? I see a hand up for Dr. Crandall, but I'm not sure if that's left over from the previous discussion.

DR. CRANDALL: I just took it down.

DR. LOW WANG: Okay, great. Thanks.

So if there are no questions or comments about the wording of this question, I'd like to

open this question to discussion.

So while we're waiting for people to raise their hands, maybe I'll start. I really appreciate the studies conducted by both the applicant and the modeling that was done by the applicant and the FDA to help us understand potential risk mitigation strategies while maintaining efficacy.

I would say that because this trial was done, everyone was on CGM, and then we had this dosing and titration strategy, we still see this difference in risk of hypoglycemia. So I think that, actually, the initial dosing and titration strategy doesn't seem to be adequate to bring the number and rate of hypoglycemia down to what was observed with the once-daily basal, but the modeling does seem to support the idea that reducing bolus insulin doses on days 2 through 4 would be helpful to mitigate risk. It complicates insulin dosing a lot and would be anticipated to increase medication errors, and this is in addition to changes in bolus insulin dosing that patients have to make any way for changes in activity and

illness, weight changes, other factors, so I'm concerned about that.

But I would like to move on to Dr. Beringer. Go ahead.

DR. BERINGER: Yes. I think I stated earlier the modeling, I think, predicted well the fasted glucose at week 26 and the amount of glucose control that was there. I think when they applied it to look at alternative dosing regimens, I think it clearly did show a substantial reduction in the amount of hypoglycemia by about 40 percent by reducing the the bolus insulin.

So I think the modeling assisted in finding a strategy that's been successful in reducing hypoglycemia, but I would agree, as others have stated, that the main benefit of this therapy is going once a week from once a day. It's a convenience thing that makes the regimen less complicated, but if you now have to monitor on days 2 through 4 and make adjustments to your bolus regimen, that's a trade-off in terms of the complication for the regimen, so it may not be as

convenient for the user in that regard.

DR. LOW WANG: Perfect. Thanks.

Mr. Tibbits?

MR. TIBBITS: Paul Tibbits. I think I have a version of exactly what Dr. Beringer said, which it does concern me a little bit that the FDA specifically recommended to the applicant to include in their trial an arm in which icodec was dosed twice a week. When asked why that didn't happen, I think the answer essentially was it would introduce complexity, and we're trying to introduce simplicity.

But for these exact reasons that Dr. Beringer just outlined, I think by limiting the trial to once a week, because that is their intended indication, they are in fact potentially including complexity and didn't investigate an avenue, which I would argue if you have to do multiple bolus doses and calculations over 3 days, that might actually be more complex than doing one basal twice a week. So I'm a little uncomfortable with the approach that was taken in terms of

deciding not to test the twice-a-week dosing strategy.

DR. LOW WANG: Thank you.

Dr. Onumah?

DR. ONUMAH: Barbara Onumah, a similar comment about the complexity of the modeling and suggested dosing, and also to comment about potential providers who may be prescribing insulin icodec not necessarily being expert persons who manage diabetes, so for the general clinician who may not be an expert in managing diabetes and the confusion that it might create.

DR. LOW WANG: Thank you so much for those comments.

Dr. Crandall?

DR. CRANDALL: Yes. I just want to agree with what was said about the increasing complexity of having to adjust the bolus dosing on certain days of the week. I think it's challenging, to begin with, to come up with accurate bolus dosing for many patients, and I don't see this as a practical -- as was mentioned I guess in the

comments from investigators in the trial, some patients just kind of naturally did this, and those are the patients who are very comfortable, and familiar, and motivated to take an active role in their management, but that's not every patient. That's not even most patients, at least in my experience, and I think it's a very challenging thing to come up with the right dosing for bolus, and I think this will only make it more complicated. And I also was disappointed or not very satisfied with the response about the twice-weekly dosing for the reasons that were just mentioned.

DR. LOW WANG: Thanks.

Dr. Kalyani?

DR. KALYANI: Thanks. Rita Kalyani. I would say that the theoretical models that demonstrated reducing the dose by 30 percent during days 2 to 5 was most effective, predicted in reducing the hypoglycemic events, and did support that that could be a strategy that's used. It was a modeled approach, so we don't have actual data

from the trial that we know that some participants did that on their own.

I would say, which I brought up earlier, that the dosing and titration regimen used in the trial was a weekly dosing and titration regimen, and in practice, we would probably titrate the medications at both the basal and the prandial, similar to our other insulins, every 2 to 3 days. So perhaps it wouldn't be adding more complexity, necessarily, compared to the existing insulins, but I do think this idea that on some days you have to decrease the insulin and on some days you have to increase the insulin, that does add some element of complexity and introduce the potential for errors as well.

So I think there are both sides; that while the trial did have a titration regimen, that in practice, actually, for the really motivated participant or the person that we're able to see more often, we might recommend a titration regimen that's even every few days, but to have someone always reduce it on a certain day and always

increase it on a certain day, it does seem like it could be challenging for some.

DR. LOW WANG: Thank you for those comments.

Any other comments from the panel?

(No response.)

DR. LOW WANG: So let me try to summarize our discussion. As with my previous summary, additional comments from the panel members on this discussion summary are appreciated. I think what I heard is that the modeling does help us understand the potential effect of the risk mitigation strategies, specifically reducing the doses of bolus insulin on days 2 through 4, but what was mentioned is that reducing complexity of a treatment regimen by reducing the number of basal insulin doses is balanced by increased complexity of having to change bolus insulin doses on certain days of the week; so are these bolus dosing changes able to be done accurately, and then also having clinicians with less experience advise on this. Then there was also concern expressed about not testing the twice-a-week dosing strategy for

insulin icodec.

Any other comments to add to that summary?

(No response.)

DR. LOW WANG: Okay. So if there are no further comments on that, then let's move on to question 4, which is also a discussion question, so slide 5, please. Again, I'll ask for comments or questions on the wording after I read the question. This fourth discussion question is, discuss the role of insulin icodec in the context of the available treatment armamentarium to improve glycemic control in patients with type 1 diabetes.

Any questions about the wording?

(No response.)

DR. LOW WANG: Alright. If there are no questions or comments about the wording, we'll open the question to discussion. I think we may not have heard from all of the members of the panel, so I'd love to hear from you if you haven't spoken yet, in addition to everyone else who's been very engaged. Thank you.

We do have raised hands, so Dr. Dutta, go

ahead.

(No audible response.)

DR. LOW WANG: I think you may still be muted.

DR. DUTTA: Hello. This is Sandeep Dutta, and I do want to make some comments. I think it's related to both discussion question 1, as well as this one. I do believe that this product provides an incremental innovation and provides a choice and convenience to patients and prescribers. As has been recognized by many today, including the applicant, this is not a product for every patient. I also acknowledge that the specific subpopulation who benefit have not been clearly identified and studied in a randomized manner.

Nevertheless, I believe the prescribers and patients will learn to use this product such that they can mitigate the risk of hypoglycemia with appropriate strategies, particularly compared to what was observed in this study, which showed significantly high risk compared to other basal insulin products, and the comparator basal insulin

product used has the lowest hyperglycemia risk. So overall, I think the benefit outweighs the risk, so this product would be an important choice for some patients and prescribers. Thank you.

DR. LOW WANG: Thank you for those comments.

Dr. Drake?

(No audible response.)

DR. LOW WANG: Sorry. I think you're still muted. Go ahead, Dr. Drake.

DR. DRAKE: Well, specifically as it relates to this question, I applaud them for going head to head against insulin degludec. I think that really is considered the gold standard. Insulin glargine, when it came around, it was really titered as a 24-hour insulin. I think that it is for some patients, but for many patients, it's so much short of that. It's a particular problem in type 1 diabetes, where we actually use it often twice daily to achieve these effects. But that said, insulin degludec really is an insulin that does last for at least 24 hours, so I applaud them for going up against insulin degludec because I think

it's a tough challenge.

That said, insulin degludec works quite well. We saw the data that was presented today that it's really quite stable across days, and there isn't this day 2 to 4 challenge that will almost certainly come to bite some patients with type 1 diabetes. I do worry about the patients who would really benefit from once-weekly insulin, and there's certainly some who are not fantastic, and we have those in our clinical practice, but those are also the patients who don't regularly monitor. So it would require those patients to monitor more regularly and/or have a concomitant CGM as a qualifier. So to have this medication prescribed is going to be a tall order, I think, for some patients. So it's an interesting molecule, but I'm not sure exactly where it fits in the current armamentarium for patients with type 1 diabetes, specifically.

DR. LOW WANG: Thank you for those comments.

Dr. Weber?

DR. WEBER: Yes. To follow up on

Dr. Drake's comments and mostly the discussions, there are a couple of things that I wanted to comment on. One is, we've been talking about hypoglycemia, and certainly unconsciousness and attention and treatment obviously are pretty significant, but I was trying to look globally at what other risks there may be, and I was thinking cardiovascular risk in particular. I don't think we have a lot of data that the risk for cardiovascular outcomes has increased with hypoglycemia in type 1 as it is in type 2 in the ACCORD study, so that's one thing to think about. But where it fits in the whole armamentarium is a good question, and there's clearly a need, and I think it's a risk-benefit trade-off that we're going to look at.

One comment on the twice-weekly proposal, which was proposed, I would wonder whether or not, in that sort of approach, there would be a staffing phenomenon as we see with other types of insulins. So perhaps there's a safety issue there as to why that was not pursued, and I'm not sure if that was

mentioned, but again, I'm just trying to sort out where things are. This is going to be a therapy that some folks with type 1 diabetes would be very helpful for, but navigating that with a strategy is what's in play.

DR. LOW WANG: Thank you.

So let me maybe add my comments. I don't see any other raised hands yet. I think the availability of a once-weekly insulin would be an important addition to the armamentarium for type 2 diabetes. I think we saw data to show that, even though today's focus is really type 1. I think that it's more questionable in type 1 diabetes because of this added complexity of the therapy, increased risk of hypoglycemia without demonstrated improvement, and adherence or treatment satisfaction, or what the effects are of the proposed risk mitigation strategies outside of the modeling.

So we understand that managing diabetes with insulin is incredibly complex, and adding an additional factor of trying to remember what day

number it is and what to do with bolus insulin doses just adds to that complexity. So I'm concerned about that, even though, in general, I think it's important to try to add more tools to our toolbox for our patients.

Any further comments on this discussion question?

(No response.)

DR. LOW WANG: So if there are no further comments, then let me summarize our discussion as best I can. I think what was commented on is that insulin icodec is an important addition to our toolbox, but it's not for every patient. I think the panel members plotted the comparison with insulin degludec in the clinical trial rather than a different basal insulin, but noted that it's a challenging insulin to use for our patients with type 1 and not sure where it fits into the armamentarium for type 1. There's the added complexity of the therapy, the increased risk of hypoglycemia, and then no demonstrated improvement in adherence, treatment satisfaction, or the actual

effects of the proposed risk mitigation strategies.

Any points I've missed there?

(No response.)

DR. LOW WANG: So we are running a little ahead of schedule, but I think this is great. So if panel members agree, we can proceed to question 5, which is the voting question. Commander LaToya Bonner will provide the instructions for voting.

CDR BONNER: Thank you, Dr. Low Wang.

LaToya Bonner, DFO. Question 5 is a voting question. Voting members will use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you will be removed to a breakout room while we conduct the vote. After the chairperson reads the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin.

A voting window will appear where you can submit your vote. There will be no discussion during the voting session. You should select the

button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote is closed.

Please note that there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list, and each voting member will state their name and their vote into the record. Voting members should also address any subparts of the voting question, including the rationale of their vote.

Are there any questions about the voting process before we begin?

(No response.)

CDR BONNER: Since there are no further questions, I will hand it back to Dr. Low Wang so we can begin the voting.

DR. LOW WANG: Okay. Thank you.

Question number 5 is our voting question. Based on the available data, has the applicant demonstrated that the benefits of insulin icodec outweigh its risks for improving glycemic control in adults with type 1 diabetes? If yes, explain your rationale and comment on any risk mitigation measures you believe would be necessary to ensure that the benefits outweigh the risks. If no, explain your rationale and comment on additional data that could be provided to demonstrate that the benefits outweigh the risks.

Are there any specific questions? It looks like there's a specific question about the wording of the voting question, so, Mr. Tibbits, go ahead.

MR. TIBBITS: Thank you. Paul Tibbits.

Dr. Low Wang, I don't know if this is for you and your interpretation of the question or for the FDA, but in thinking about the benefits and risks for adults with type 1 diabetes, is the FDA looking for us to answer in the context of what the label might look like, meaning do we think that

this could be a broad label for all of those with type 1 diabetes, or are they looking for a more -- I mean, obviously, a yes/no vote is yes/no, and that can't be nuanced; so just a little bit more guidance about how this might translate into a label and a lot of the discussion we've had about potential mitigation strategies.

DR. LOW WANG: I'll start with my answer and then also ask the FDA to weigh in. I think what you vote is important, but I think your rationale for the vote, and risk mitigation measures, and additional data you might like to see are all really important aspects of this vote and kind of the explanation afterwards, and would be informative to the agency, as I understand it.

So I'd like to ask the FDA to respond.

DR. ARCHDEACON: This is Patrick Archdeacon. I'll, again, endorse what our chair is saying. I think as important as the actual vote tallies are the discussion. I do think what we're asking in this question is for the panelists to tell us whether or not they think this product is

approvable in adults with type 1 diabetes; and if so, by what mitigation strategies? That would include comments specifically on labeling that you think is necessary to make the benefit outweigh the risk and/or any other measures that you think would be appropriate outside of labeling.

DR. LOW WANG: Mr. Tibbits, did that answer your question?

MR. TIBBITS: Yes, that's extremely helpful. Thank you.

DR. LOW WANG: Okay. Terrific. Great.

Any other questions?

(No response.)

DR. LOW WANG: Okay. It looks like there are no further questions or comments about the wording of the question, so I'll turn the meeting back over to Commander Bonner so that we can begin the voting on question 5.

CDR BONNER: Thank you, Dr. Low Wang.

We will now move non-voting participants to the breakout room.

(Voting.)

CDR BONNER: Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

CDR BONNER: LaToya Bonner. For voting question 5, 4 yeses, 7 noes, 0 abstentions.

DR. LOW WANG: Thank you.

Now we'll go down the list and have everyone who voted state their name and vote into the record, and please include the rationale for your vote, and we'll start with Dr. Drake.

DR. DRAKE: Okay. Matthew Drake. I voted no. My rationale is that when compared to the current gold standard degludec, it has a good safety profile in my experience, and based on review of the data today, this was an incremental increase. I am also concerned about the potential that this would need to be approved with contingencies, specifically need for CGM, so that makes me nervous. Also, the patients who may be most likely to benefit from this in my clinical experience in practice are, unfortunately, the ones who tend to be the least likely to actually monitor

their blood sugars with some regularity.

DR. LOW WANG: Thank you.

Dr. Kalyani?

DR. KALYANI: Thanks. I voted yes. Results from the ONWARDS 6 trial demonstrated that the primary outcome of A1c lowering efficacy of insulin icodec is noninferior to insulin degludec in people with type 1 diabetes; however, important concerns were raised regarding the higher percentage of participants with hypoglycemia events, particularly level 2, and higher serious adverse events, which are mostly related to severe hypoglycemia in the insulin icodec arm.

Nonetheless, many dose titration strategies were modeled, including reduction of bolus insulin by 30 percent in days 2 to 4, which suggests a reduction of hypoglycemia events and comparable A1c efficacy. Further, those who had hypoglycemic events in ONWARDS 6 seemed to be the ones to be more likely to have frequent recurrent events in the icodec arm and could potentially be flagged as people who would not benefit from this treatment in

the future.

As a once-weekly insulin icodec offers a new paradigm for insulin administration, which may reduce treatment burden and facilitate medication taking behavior for some individuals with type 1 diabetes, on the other hand, bolus dose adjustments required to prevent hypoglycemia during days 2 to 4 and potentially prevent hyperglycemia in days 5 to 7 may add to the treatment complexity.

The clinical trial did not offer the option to titrate insulin doses beyond weekly, though some participants did this on their own, which may also not reflect real-world situations where doses can be adjusted every few days to mitigate glycemic variability. In the context of patient-centered care, insulin icodec offers a new option for people with type 1 diabetes to obtain optimal care, but may not be a simple option for all people with diabetes.

Label considerations include adding the need for continuous glucose monitor, or self-monitor blood glucose if not available, while taking icodec

and warning for the higher risk of hypoglycemia with insulin icodec versus degludec, and to avoid use in those with higher risk of hypoglycemia, such as those who are older, renal comorbidities, or with high glycemic variability as measured by percent CV or standard deviation until we have more data to support use in these populations.

Clinical considerations include a need to identify those that can take icodec safely and who most obtain benefit such as those with suboptimal medication taking behavior, fear of injections, or unpredictable schedules. There needs to be guidance for reducing bolus insulin during days 2 to 4 during its peak effect.

Given the PD profile, tighter A1c targets may be more difficult to obtain without resulting in higher rates of hypoglycemia. It is also important to consider switching to daily basal insulins in those who demonstrate recurrent hypoglycemia while on icodec. Icodec, however, may further offer a transition insulin for those who have not been able to consistently take basal bolus

regimens daily and to lower A1c and potentially prevent DKA in those at high risk of missing daily insulin injections.

We do need more studies regarding patient-reported outcomes among people with type 1 diabetes. Further evidence regarding subgroups that would most benefit from the option of weekly insulin can help guide the use in practice, and also more studies regarding dose titration schedules would be helpful.

However, overall, given that the primary outcome for A1c efficacy has been demonstrated as noninferior to insulin degludec; that risk mitigation strategies to prevent and identify hypoglycemia in a timely manner are available, ideally through CGM or quantitatively self-monitor blood glucose; and that effective treatments for hypoglycemia are readily available, guided by the compelling need to offer people with diabetes another treatment option to choose from as part of patient-centered care, my vote is yes.

DR. LOW WANG: Thank you, Dr. Kalyani.

Mr. Tibbits?

MR. TIBBITS: Paul Tibbits. I voted yes. This was a significant struggle for me. I use my guide as the FDA's response to my question about clarifying the wording, the response being we want to know if this is approvable. So my answer is still yes, but I would answer that, in my mind, it is only approvable with significant caveats and what I would say would be potentially some of the more draconian limitations the FDA could put on it, meaning certainly some of the issues we've discussed, which would not be a surprise, but CGM involvement in the label; potentially glycemic variability; certainly excluding patients from the indication who have hypoglycemic unawareness; and relating to something Dr. Onumah raised earlier, I think, patients in their first year of diabetes potentially excluded from the label.

As a patient representative, I certainly want to help people with diabetes, but I also don't want to hurt them, and I think this product has the potential to do both. So I would put the onus on

the FDA to work with the applicant to make sure that if this is approved, that there are as many guardrails as possible to make sure that we don't harm people with type 1 diabetes.

I would also take this moment to say that, in my time in the healthcare world as a professional, I did work on patient-reported outcomes and patient data, and it's a little bit disappointing that a company of this stature in the diabetes world did not either present or do more diligent work in specifically the type 1 community and this product, knowing that this is where some of the risks were and some of the controversy would be, and to have a deeper understanding of who in the type 1 world would really benefit; what is the target audience; how do we work with the target audience; and how do we work with the community to ensure that this is really reaching the people who it could most benefit?

I would also add that I would urge the FDA to be extremely creative if they were to approve this. Again, I'm very uncomfortable with the idea

of imposing something like a CGM restriction to people who may already have access issues, so to see if there's a creative way to tie that requirement to something that the applicant would need to do to ensure that whoever does get this product is also able to access it without creating additional burden for the patient, him or herself. So again, I voted yes, but with significant caveats and reservations.

DR. LOW WANG: Great. Thank you.

Dr. Weber?

DR. WEBER: This is Tom Weber. I voted yes. It was also a very tough call. I went back and forth, but I think what I landed on was the big picture; that I think and believe there is more benefits than harm. I think there is a population of patients who will benefit from weekly therapy, understanding there are challenges to mitigate the risk of hypoglycemia, which is real. And I do think if it is approved, there should be a dedicated effort, obviously, for both direct-to-consumer and physician education on

insulin dose adjustment and strategies to mitigate that risk.

As mentioned earlier, as well, we do have strategies to treat hypoglycemia, including nasal glucagon, so there are ways to mitigate and treat if it occurs. But I think, big picture, overall it will be important to have this in our toolbox and armamentarium for the reasons discussed, but obviously there are things to work out and to do this in a safe manner.

DR. LOW WANG: Thank you.

Next is Dr. Brittain, and just a reminder, if you could also comment on additional data that you think could help demonstrate that the benefits outweigh the risks.

DR. BRITTAIN: I'm Erica Brittain, and I voted no. It was a hard decision, the fact that we didn't see any actual benefit demonstrated relative to the comparator in the trial, which was important to me because the question I think literally said something to that effect; have we seen the data that shows the benefit? But again, the

hypoglycemic risk that was shown was not balanced by any data on satisfaction scores that were encouraging, and even though the scores may be very flawed, it was discouraging that I didn't see that.

There was a lot of talk about what's really the right population, and it's not clear that this trial really matched the appropriate population, so I'm going to wonder about the generalizability of this trial to the people who would be the most natural audience or target for this treatment.

Again, I'm pretty optimistic that there's a way forward for this once-a-week treatment in type 1, but I think there just needs to be another study in the right population that shows that the risk of hypoglycemia can be managed in that right population. Thank you.

DR. LOW WANG: Thank you.

Next, Dr. Crandall, and just a reminder to comment on what additional data you think are needed.

DR. CRANDALL: Jill Crandall. I voted no. I think it's very clear about the benefits of

icodec or once-weekly insulin in type 2 diabetes patients. I'm very happy about that prospect of that being available, but I don't really feel like the company did a good enough job of demonstrating the benefits in type 1 diabetes. As I said earlier, I think the risks are very clear, the benefits are not. I think specifically in the area of patient satisfaction, I'd like to see more data. I'd like to see more attention paid to the experience of patients who are using the drug, and I think in future studies, that that's something that would be very important.

I also think that future studies should test out the hypoglycemia mitigation strategies that they talked about. One of the main hypoglycemia mitigation strategies was use of CGM, but CGM was used in this study, so I think they need to do more and test the modeling that they did that suggested that the bolus adjustments would deal with the hypoglycemia. I mean, even if that turns out to be true in an actual clinical trial, I still have reservations about the applicability of that for

many patients with diabetes.

I guess that gets to the final issue, which is it's still not completely clear to me what the target population for this drug would be. I agree with Dr. Brittain; I'd like to be optimistic about it. I think there are some theoretical benefits, but I think there needs to be more work done targeting what is the population that could benefit and how do we mitigate the risks of hypoglycemia.

DR. LOW WANG: Thank you.

Dr. Nason?

DR. NASON: This is Martha Nason. I voted no. Everything that I had on my list to say somebody has already said, so I feel very unoriginal. But I suppose that's good in saying that we have some consensus and that we all have some of the same ideas and concerns.

I think if they have learned from this study what they think would be good strategies for selecting subgroups, maybe on the CV or something else, for titration or mitigation, I think it would be really important to then put those to the test

with another clinical trial and be able to show that they are able to increase the safety or find the people in whom the safety seems to outweigh -- sorry, the other way around, the benefit seems to outweigh any safety concerns, whether it's low CV or something else.

I basically agree that this has promise and I hope it will work out. There just seems to be a little more information needed as far as really pinning down who and how it's used. Thanks.

DR. LOW WANG: Great. Thanks.

Dr. Onumah?

DR. ONUMAH: I voted yes. Barbara Onumah. My rationale was based on the fact that this would add a tool to the toolbox for clinicians to use their clinical judgment because it is not very apparent which specific population this would work in, but there is a subgroup of patients, using clinical judgment as we have discussed, that this would be beneficial for.

The questions that we were tasked with, or the question that we had to answer was, is there a

group that will benefit or have they shown that there would be a glycemic benefit or improvement? And my answer is that, yes, there would be in the subgroup of patients who are not able to use once-daily insulin for whatever reason and therefore have suboptimal glycemic control. If they're able to get access to a once-weekly basal insulin, then they would have improved control and they will have improvement in the glycemic control.

Of course, we still worry about hypoglycemia, which is what we worry about when we use any forms of insulin, but certainly there are lots of questions and lots of risk mitigation that, should this move forward, I would hope would have to be addressed and answered. We would certainly need more studies regarding dose titration, and we will also definitely need a lot of both patient and provider facing education material as it pertains to how to prevent, and treat, and adjust doses, and how to prevent hypoglycemia specifically, but most importantly how to adjust dosing so that we can prevent the hypoglycemia from occurring.

On the grand scheme of things, I think it's always important to have more tools to choose from, and because we know that diabetes is not a univariable disorder and it's very different in every person that we see, it's important and it's helpful when we have different tools that we can use to address every single person. And this data that we have reviewed today, while this is not very robust in terms of comparing it to what we already have, it was not inferior to what we already have, so it does show some promise in terms of using it in persons who are not able to use what we have currently; thus, my vote for yes.

DR. LOW WANG: Thank you so much.

Dr. Greevy?

DR. GREEVY: This is Robert Greevy. I voted no, the benefit-risk difference for insulin icodec has not been shown to be positive in the ONWARDS 6 trial; however, the data does suggest, and many speakers attested, that there may be a specific subpopulation who would benefit from icodec. A lot of us in speaking so far have really suggested that

we have a sense that there's this group, but the sponsor bears the burden of clearly identifying that subpopulation and demonstrating the benefits in that group.

It's not clear that the subpopulation is simply those with low hypoglycemic risks and who use CGM. Notably, those criteria don't address the key motivation for a once-weekly therapy specifically, or adherence with daily injections, or great aversion to these daily injections, so it seems like there should be some work done to identify the subpopulation that we all seem to think is out there.

An exploratory post hoc analysis of those who reported being highly satisfied or highly dissatisfied with their treatment in the ONWARDS 6 data could provide some insights. Excluding this subject with 30 hypoglycemia events, did hypoglycemia events associate with loss to follow-up, with satisfaction or other patient-reported outcomes, with 52-week A1c?

One of the things the data hinted lightly

at, or at least sparked my curiosity, is with this increased risk of hypoglycemia over time, did that result in a growing dissatisfaction with icodec, and maybe even a reduction in how well people were using icodec such that the A1c performance itself seemed to be a little bit reduced at 52 weeks?

Follow-up studies on the ONWARDS 6 trial participants, or specific subgroups of those participants, could also be considered. Notably, this would include patients who had to switch, due to the trial ending, from icodec to a different therapy, possibly daily insulin. So what did they switch to? How did it go following 6 to 12 months after the end of the ONWARDS 6 trial? How does the group who were highly satisfied with icodec compare to the group who are highly satisfied with degludec? I think those questions could really offer a lot of insight into who this subpopulation might be.

My final thought on possible data that wouldn't be too hard to get but could be really interesting is a post-study survey of the icodec

arm, who would and would not be willing to go back on icodec if they were offered that opportunity and why, and what characterizes those who would go back on it? Thank you.

DR. LOW WANG: Great. Thank you.

Dr. Beringer?

DR. BERINGER: Paul Beringer, and I voted no basically on the risk-benefit ratio. The benefits of the therapy are clearly once-weekly administration would be easier to do, but that's likely to be offset by the increased treatment complexity by having to monitor and adjust bolus doses on days 2 through 4.

Secondly, the PK/PD modeling data do not support once-weekly administration as evidenced by the glucose response variability that we saw during the week, and it's also confirmed by the higher risk of hypoglycemia as seen in the ONWARDS 6 trial. The proposed risk reduction strategies are untested and may be difficult to implement in practice. And as stated by others, I think going forward, it would be beneficial to actually test

those risk mitigation strategies in a trial to see whether, in fact, they can be implemented and the goals can be achieved in the patients.

DR. LOW WANG: Great. Thank you.

I think I'm last. My name is Cecilia Low Wang, and I voted no. I struggled with this vote because I think adding more treatment options, as has been mentioned, is super important for my patients with diabetes, especially my patients with type 1 diabetes because that's kind of an under-investigated area right now, different medication treatment options.

I'm concerned that approving icodec for use at this point, with inadequate data, might be a disincentive for further trials, which I think are needed in order to use it safely in type 1 diabetes. I'm concerned about the lack of data outside of the modeling that demonstrates that the proposed risk mitigation strategies will be effective for reducing the significantly increased risk of hypoglycemia that was demonstrated. We also saw post hoc data regarding the lower risk of

hypoglycemia in patients with lower coefficient of variability, but this was post hoc.

I think more data are needed, specifically regarding a protocol for decreases in bolus dosing on days 2 to 4 and identifying populations who would benefit the most from this insulin. And just a reminder that the ONWARDS 6 clinical trial included fewer than 300 patients with type 1 diabetes, and we really don't have adequate data regarding efficacy of, again, those risk mitigation strategies, and then subgroups of patients with type 1 diabetes who would most benefit; so the patients with a lower coefficient of variability and how to do without CGM.

I think I'd like to summarize the committee's comments before we end. We had four panel members who voted yes and seven who voted no. What I heard was a consensus that insulin icodec could benefit some patients with type 1 diabetes to be able to individualize therapy, and it was noted that the clinical trial met the primary endpoint of noninferiority for reduction in A1c. There was

really a lack of consensus on adequacy of the demonstrated benefit. Many of these other potential benefits were described as theoretical in our prior discussions.

Panel members felt that adding to our treatment options was felt to be very important for our patients, but that the risks of hypoglycemia were significantly greater than with the comparator and didn't necessarily outweigh the added complexity that was seen. The question of what is the best treatment population was kind of noted over and over, and it might be that it would be those who can't use once-daily insulin, and because of that have suboptimal control.

Some suggestions for labeling included restricting use from those who are within that first year of type 1 diabetes, those who are at higher risk of hypoglycemia, including those who are older with decreased kidney function, higher coefficient of variability, recurrent DKA, or recurrent hypoglycemia. It was noted that the panel members would like more treatment options

with less variable pharmacokinetics for our patients with type 1, and also that there's a lot of patient and clinician education needed for its use if it's approved.

The further data that are needed included patient satisfaction information; efficacy of the hypoglycemia risk mitigation strategies; a bolus dose titration protocol; and then which subgroups of patients with type 1 diabetes who would most benefit from its use. We need more information on the safety in patients with lower coefficient of variability and whether we can use it in patients with type 1 without the use of CGM. It was also mentioned that follow-up studies from ONWARDS 6 would be helpful in terms of what insulin was switched to, and then is the satisfaction with the therapy durable?

Now, I think we're at the end of our time here, and I'd like to express my sincere appreciation for the work that went into preparing for and organizing this meeting by all involved, and I thank each of the panel members for your

time, your expertise, and the robust discussions. I'd like to thank Novo Nordisk and the FDA for your concise and informative presentations, as well as Commander Bonner and the staff at the FDA for preparing for this meeting. I'd like to thank the individuals who spoke during the open public hearing for your important contributions to the meeting, and lastly, to the members of the public for attending.

So before we adjourn, are there any last comments from the FDA?

DR. NGUYEN: Hi. This is Dr. Michael Nguyen. I just wanted to thank the panel for convening today and sharing all of your clinical, statistical, and personal experiences on this important topic. I also wanted to thank you for sharing very, very specific and very helpful recommendations on what additional data would be needed for this product. I also wanted to thank Dr. Low Wang, especially, for chairing and making this a very effective and efficient meeting. Thank you and enjoy your long weekend.

Adjournment

DR. LOW WANG: Thank you so much. We will now adjourn the meeting. Thank you, everyone.

(Whereupon, at 4:04 p.m., the meeting was adjourned.)