Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 24, 2024

Location: All meeting participants will be joining this advisory committee meeting via an online teleconferencing platform.

Topic: The Committee discussed the safety and efficacy of biologics license application 761326 for NNC0148-0287 injection (insulin icodec), a long-acting insulin analog product, submitted by Novo Nordisk. The proposed indication is to improve glycemic control in adults with diabetes mellitus.

These summary minutes for the May 24, 2024 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on July 25, 2024 .

I certify that I attended the May 24, 2024 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/

LaToya Bonner, PharmD
Designated Federal Officer, EMDAC

/s/

Cecilia C. Low Wang, MD
Chairperson, EMDAC

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 24, 2024

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on May 24, 2024. The meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Novo Nordisk. The conflict-of-interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There was approximately 2942 people online. There was a total of 6 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:

The Committee discussed the safety and efficacy of biologics license application (BLA) 761326 for NNC0148-0287 injection (insulin icodec), a long-acting insulin analog product, submitted by Novo Nordisk. The proposed indication is to improve glycemic control in adults with diabetes mellitus.

Attendance:

EMDAC Members Present (Voting): Matthew T. Drake, MD, PhD; Robert Alan Greevy, Jr., PhD; Rita R. Kalyani, MD, MHS; Cecilia C. Low Wang, MD *(Chairperson)*

EMDAC Members Not Present (Voting): Michael Blaha, MD, MPH; Thomas Wang, MD

Acting Industry Representative to the Committee (Non-Voting): Sandeep Dutta, PhD (Acting *Industry Representative*)

Temporary Members (Voting): Paul Beringer, PharmD; Erica Brittain, PhD; Jill P. Crandall, MD; Martha Nason, PhD; Barbara Onumah, MD; Paul Tibbits, Jr. (*Patient Representative*); Thomas J. Weber, MD

FDA Participants (Non-Voting): Lisa Yanoff, MD; Patrick Archdeacon, MD; Michael Nguyen, MD; Frank Pucino, PharmD, MPH; Leslie Kenna, PhD; Roberto Crackel, PhD; Jaejoon Song, PhD; Elyes Dahmane, PhD

Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD

Open Public Hearing Speakers Present: Julie Heverly (diaTribe Foundation); Azza AbuDagga, PhD (Public Citizen's Health Research Group); Thomas Danne, MD (Juvenile Diabetes Research Foundation International); Kelly Close (Close Concerns) Alan Beltran,

Andrew Goyette, and Mahima Chillakanti (dQ&A); Sethu Reddy, MD, William Biggs, MD, and Janet McGill, MD (American Association of Clinical Endocrinology)

The agenda was as follows:

Call to Order	**Cecilia Low Wang, MD** Chairperson, EMDAC
Introduction of Committee and Conflict of Interest Statement	**LaToya Bonner, PharmD** Designated Federal Officer, EMDAC
FDA Introductory Remarks	**Michael Nguyen, MD** Cross Discipline Team Leader Division of Diabetes, Lipid Disorders, and Obesity (DDLO) Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN) Office of New Drugs (OND) CDER, FDA
APPLICANT PRESENTATIONS	**Novo Nordisk**
Introduction	**Shawn Hoskin, MS** Executive Director, Regulatory Affairs Novo Nordisk
Unmet Need for Basal Insulin Treatment	**Ildiko Lingvay, MD, MPH, MSCS** Professor of Medicine Department of Internal Medicine/Endocrinology UT Southwestern Medical Center
ONWARDS Development Program and Icodec Dosing	**Stephen Gough, MD, FRCP** Global Chief Medical Officer Senior Vice President Novo Nordisk
Safety of Once-Weekly Injection of Insulin Icodec	**Roman Cailleteau, MD** Senior Medical Director Novo Nordisk
Efficacy and Hypoglycemia in Participants with Type 2 Diabetes	**Roman Cailleteau, MD**
Efficacy and Hypoglycemia in Participants with Type 1 Diabetes	**Stephen Gough, MD, FRCP**
Clinical Perspective	**Idiko Lingvay, MD, MPH, MSCS**

Conclusion	**Stephen Gough, MD, FRCP**
Clarifying Questions to Applicant	
BREAK	
FDA PRESENTATIONS	
Clinical Pharmacology Assessment of Insulin Icodec	**Leslie Kenna, PhD** Clinical Pharmacology Reviewer Division of Cardiometabolic and Endocrine Pharmacology (DCEP) Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS) CDER, FDA
ONWARDS 6: Study Design	**Frank Pucino, PharmD, MPH** Clinical Reviewer DDLO, OCHEN, OND, CDER, FDA
ONWARDS 6: Summary of Efficacy	**Roberto Crackel, PhD** Statistical Reviewer Division of Biometrics II (DBII) Office of Biostatistics (OB) OTS, CDER, FDA
ONWARDS 6: Safety Review	**Frank Pucino, PharmD, MPH**
Exploratory Analysis of Percent Coefficient of Variation (%CV) Subgroup	**Jaejoon Song, PhD** Safety Statistical Reviewer Division of Biometrics VII (DBVII) OB, OTS, CDER, FDA
Pharmacometric Modeling of Alternative Dose Titration Strategies	**Elyes Dahmane, PhD** Pharmacometrics Reviewer Division of Pharmacometrics (DPM) OCP, OTS, CDER, FDA
ONWARDS 6: Benefit-Risk Summary	**Frank Pucino, PharmD, MPH**
Clarifying Questions to FDA	
LUNCH	
OPEN PUBLIC HEARING	
BREAK	

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the benefits of insulin icodec and the risk of hypoglycemia in adults with type 1 diabetes mellitus (T1D).

   Committee Discussion*: The Committee commented on the importance of adding more options for treating adults with type 1 diabetes mellitus (T1D); however, they regarded the potential benefits of reducing treatment burden and improving medication adherence with the use of insulin icodec as hypothetical, since there were no data to support these benefits. The committee expressed concerns about the increased risk of hypoglycemia seen in the ONWARDS 6 study among subjects with T1D, and the higher incidence of serious hypoglycemia related adverse events (e.g., loss of consciousness and requiring assistance from medical professionals) observed in the icodec arm compared to control. The Committee questioned who would benefit the most from insulin icodec and noted that insulin icodec was not evaluated in patients who might stand to benefit most from a once-weekly basal insulin (e.g., patients with difficulty adhering to daily basal insulin dosing and experience recurrent diabetic ketoacidosis). Laslty, the Committee commented on the difficulty of translating the clinical trial data from ONWARDS 6 to the real world.*

   Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss the role of continuous glucose monitoring (CGM) devices and measures of glycemic variability with respect to the risk of hypoglycemia in patients with T1D using insulin icodec.

   Committee Discussion*: The Committee agreed that CGM devices are recommended for all patients with T1D and appear to be needed to mitigate the risk of hypoglycemia with insulin icodec, but strongly noted the unresolved issues of access and coverage for these devices. The Committee also acknowledged problems regarding extrapolating the risk mitigation strategies from the data. The Committee noted that there was no baseline assessment of the coefficient of variation (CV), a measure of glycemic variability. In addition, the Committee noted that there was a higher rate of hypoglycemia in the lower %CV subgroup (CV ≤36%) receiving insulin icodec compared with the same subgroup receiving insulin degludec. Furthermore it is unclear whether T1D patients with a lower %CV represent the patient population who would most benefit from insulin icodec. Some committee members noted that although glycemic variability as a general concept could be appealing, implementing this mitigation strategy in routine clinical practice is complicated by the fact that not all patients have access to CGMs or are sufficiently motivated to do self-monitoring with multiple fingersticks per day, and clinicians may be required to continually examine glycemic*

variability to prescribe the medication safely. It was noted that patients with the greatest variability may not be self-monitoring consistently, and may not be adherent to insulin therapy. Thus, the patients who could most benefit from a once-weekly insulin in terms of improved adherence may overlap significantly with the patients who may not be able to use it safely in terms of increased hypoglycemia risk.

Overall, the Committee concurred that CGM devices should be offered to all T1D patients, but its implementation alone does not eliminate the occurrences of hypoglycemia or prevent its associated adverse events.

Please see the transcript for details of the Committee's discussion.

3. **DISCUSSION:** Discuss the proposed dosing and titration regimen and the extent to which the modeling data support alternative dosing strategies.

***Committee Discussion**: The Committee commended the Applicant's efforts in implementing alternative dosing strategies using exposure-response modelling and simulations aimed at reducing the risk of hypoglycemia while maintaining efficacy in the insulin icodec arm. However, some of the panel members were not convinced by these findings as their impact has not been demonstrated in a clinical study. Several panel members also expressed concern with the Applicant's decision not to include a twice weekly insulin icodec arm in the ONWARDS 6 trial.*

Overall, the panel members agreed that the exposure-response modelling and simulations helped to understand the potential effect of the alternative dosing strategies, specifically reducing the doses of bolus insulin on Days 2 through 4. Although the dosing strategy was supported by the model, the Committee commented that insulin icodec lost one of its proposed benefits to simplify insulin administration in patients with T1D. The Committee further commented that the potential benefit of reducing the number of basal insulin doses is counterbalanced by increased complexity of having to adjust bolus doses on certain days of the week. The Committee acknowledged the challenges of determining accurate bolus dosing.

Please see the transcript for details of the Committee's discussion.

4. **DISCUSSION:** Discuss the role of insulin icodec in the context of the available treatment armamentarium to improve glycemic control in patients with T1D.

***Committee Discussion:** The Committee was undecided on the role of insulin icodec in the context of the available treatment armamentarium to improve glycemic control in patients with T1D. Overall, the Committee agreed that the specific subpopulation who would benefit from insulin icodec to treat T1D has not been clearly identified. Some panel members stated they believe that the prescribers and patients would learn to use this product such that they can mitigate the risk of hypoglycemia with appropriate strategies. Other panel members commented on the added complexity of therapy and the risks of hypoglycemia without*

additional benefits (e.g., adherence, treatment satisfaction). It was also noted that the proposed risk mitigation strategies had not been tested, and that data regarding cardiovascular outcomes were lacking.

Please see the transcript for details of the Committee's discussion.

5. **VOTE:** 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 T1D?

   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.

Vote Result: Yes: 4 No: 7 Abstain: 0

Committee Discussion: *The majority of the Committee agreed that the Applicant did not demonstrate that the benefits of insulin icodec outweigh its risks for an indication to improve glycemic control in adults with T1D. The Committee generally agreed that insulin icodec had the potential to benefit some patients with T1D; however, that subgroup was not identified and not evaluated in the clinical trial. It was also noted that the clinical trial met the primary endpoint of noninferiority for reduction in A1C, but a lack a consensus from the Committee that the demonstrated benefit outweighed the risks associated with insulin icodec in patients with T1D.*

The members who voted "No", stated that the increased risk of hypoglycemia shown in the data and the added complexity of bolus insulin dose adjustments posed safety concerns that are too clinically significant to disregard. These members noted that the theoretical benefits (once-weekly dosing) of insulin icodec did not supersede the hypoglycemia risk. Some members of the Committee recommended that the Applicant implement patient satisfaction surveys in future trials, determine the efficacy of hypoglycemia risk mitigation strategie including the bolud dose titration protocol, and overall obtain more data to help inform the benefit-risk assessment of this product. The members stressed more clinical data/information is needed to determine which subgroups of patients with T1D would benefit from insulin icodec use, and its safety in patients with lower %CV and in individuals not wearing a CGM device.

The members who voted "Yes", emphasized that the addition of insulin icodec to the armamentarium of diabetes therapies grants clinicians the opportunity to individualize glycemic control in their diabetic patients. Some members noted that the results from the ONWARDS 6 trial demonstrated that insulin icodec was noninferior to insulin degludec for the primary endpoint, change in A1C from baseline in adults with T1D, but also acknowledged the concerns raised regarding the higher percentage of participants with hypoglycemic events.

Some of the panel members suggested that the labeling include restricting use from those recently diagnosed with T1D (e.g., within the first year), the need for CGM or more frequent self-monitoring of blood glucose while taking insulin icodec, and warnings for patients at higher risk of hypoglycemia (e.g., older, decreased renal function, higher %CV, recurrent diabetic ketoacidosis, recurrent severe hypoglycemia, hypoglycemia unawareness, etc.,) In addition, patient and prescriber education on insulin icodec dose adjustments and strategies to mitigate that risk were recommended.

Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 4:04 p.m. ET.