# BLA 761326 Insulin Icodec
# Novo Nordisk

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Endocrinologic and Metabolic Drugs
Advisory Committee Meeting
May 24, 2024

# Objective of the AC Meeting

- To discuss the benefits and risks of NNC0148-0287 (insulin icodec), a once-weekly insulin analog product, for the proposed indication ‘to improve glycemic control in adult patients with diabetes mellitus.’
- The focus of the meeting will be on the safety and efficacy of insulin icodec in patients with type 1 diabetes (T1D).

# Diabetes Mellitus

- Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia and affects an estimated 38 million people in the US[1]
  - T1D accounts for 5-10% of diagnosed cases
- Management of T1D requires lifelong insulin therapy[2]
  - Continuous subcutaneous insulin infusion (CSII)
  - Multiple daily insulin injections (MDII) of a bolus and basal insulin
- Maintaining normoglycemia (hemoglobin A1c [A1C] <7%) can reduce diabetes complications
  - A1C is a biomarker that reflects the average glucose level in the previous 2 to 3 months
  - Hypoglycemia is a major limiting factor in achieving glycemic control with exogenous insulin in people with T1D

[1] National Diabetes Statistics Report. Atlanta; 2023.
[2] American Diabetes Association Professional Practice Committee. Diabetes Care 2024;47:S5-S10.

# Unmet Medical Need

- In the US, about 1/3 of adults with T1D are managed with MDII
  - 22% of adults with T1D may miss ≥1 basal insulin dose over any 14-day period[1]
  - Nonadherence is a precipitating factor for diabetic complications (e.g., diabetic ketoacidosis)
- Available basal insulin products administered 1-2x daily
- Insulin icodec is a long-acting human insulin analog intended for once weekly administration
  - In T2D, would reduce the total number of injections from 7 to 1 per week
  - In T1D, would reduce the total number of injections from 28 to 22 per week
- It is not known whether a once weekly basal insulin would improve adherence and/or glycemic control in people with T1D

[1] Ekberg NR et al. Smart Pen Exposes Missed Basal Insulin Injections and Reveals the Impact on Glycemic Control in Adults With Type 1 Diabetes. J Diabetes Sci Technol. 2024 Jan;18(1):66-73.

# Pertinent Regulatory History

## End-of-Phase 2 (EOP2) Meeting

- FDA noted that the clinical pharmacology results from the study in patients with T1D revealed that the glucose-lowering effect of insulin icodec was not constant across the dosing period, when dosed once weekly
  - FDA advised that insulin icodec may not be ideally suited for use as a once weekly product, as the proposed regimen might lead to hypoglycemia, more frequent bolus insulin adjustments and less glycemic control
- FDA agreed with an active comparator open-label study to demonstrate efficacy in T1D with the primary endpoint of A1C at 6 months
- FDA noted that meeting the prespecified noninferiority margin would not be sufficient to establish a favorable benefit-risk profile because the risk of hypoglycemia also would be taken into consideration
- FDA recommended that the Phase 3 T1D study:
  - Include a third arm to evaluate insulin icodec dosed twice weekly
  - Assess potential improvements in treatment satisfaction to offset any potential worse glycemic profile
  - Assess the potential need for additional bolus dose adjustments

# Key Issues for Insulin Icodec

- **Product**:
  - Proposed long-acting insulin analog that if administered once weekly reduces the number of basal insulin injections compared to available daily basal insulin products
  - Does not have a constant time-action profile throughout the dosing interval
- **Application findings**:
  - Insulin icodec was noninferior to insulin degludec in improving glycemic control as measured by A1C but had an increased risk of level 2/3 hypoglycemia
  - Met the regulatory approval standard for efficacy but is associated with a worse safety profile than once-daily insulin degludec
- **Applicant proposed risk mitigation**:
  - Indicate insulin icodec only for patients with low glycemic variability
  - Limit the use of insulin icodec to certain patients (e.g., adults using continuous glucose monitoring [CGM])
  - Label alternative bolus insulin dosing strategies

# Discussion Points for the Committee

## In adults with T1D:

- 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 T1D?

- 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 additional data that could be provided to demonstrate that the benefits outweigh the risks.

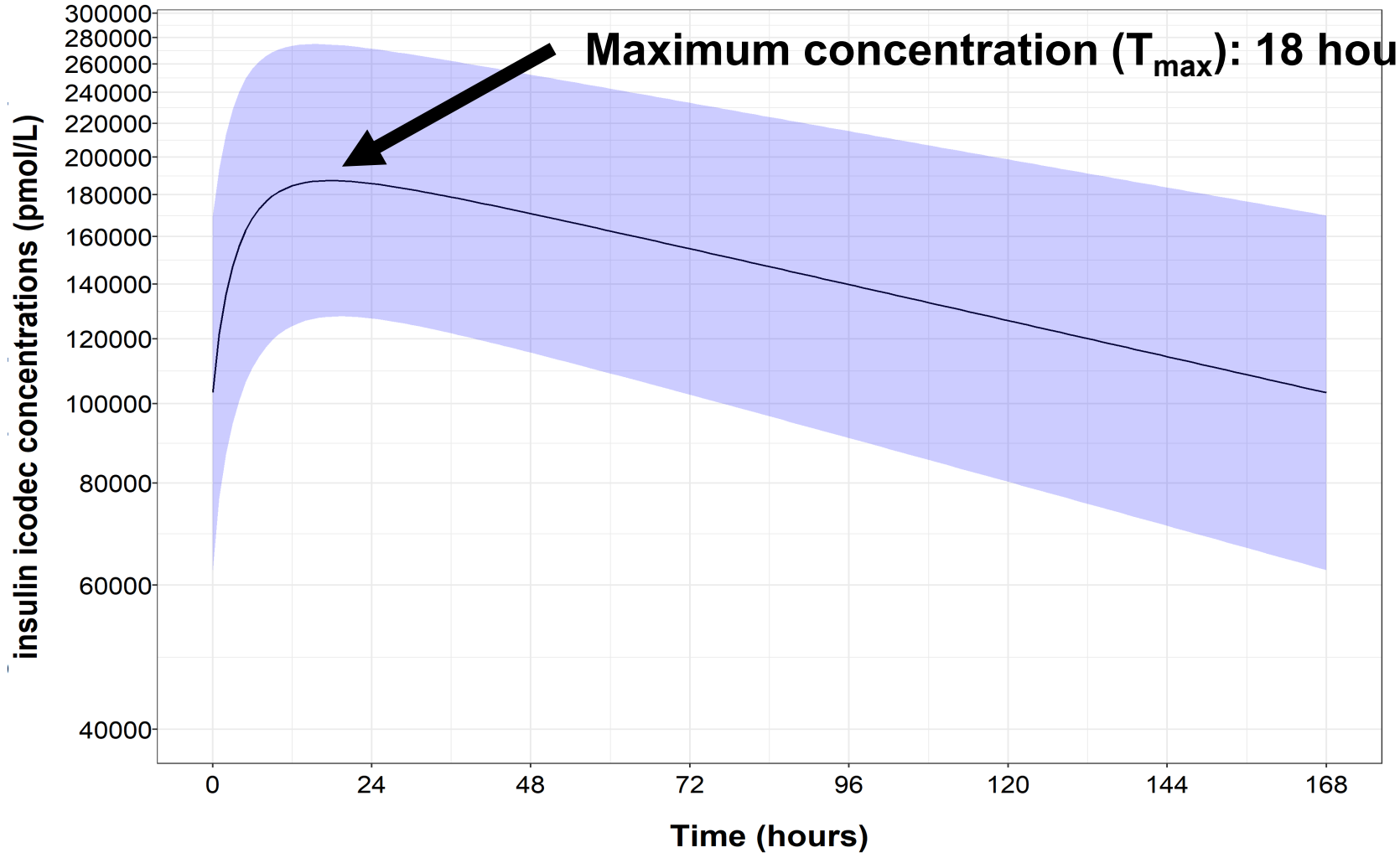
# Clinical Pharmacology Assessment of Insulin Icodec

Leslie Kenna, PhD

Senior Pharmacokineticist

Office of Clinical Pharmacology

# Pharmacokinetics of Insulin Icodec at Steady State in T1D

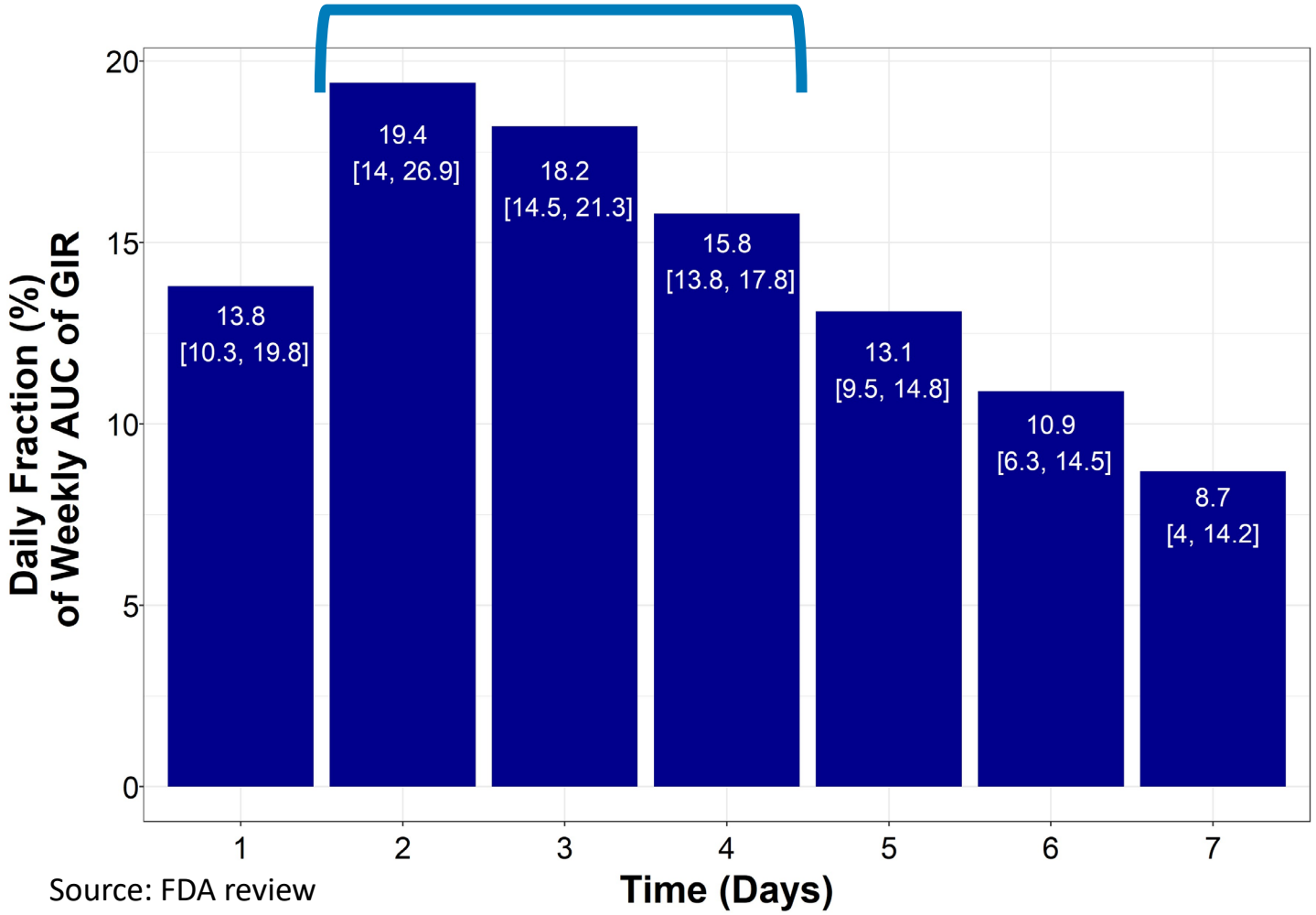



$T_{½}$: 1 week

**Source**: Independent analysis of the Applicant's PK data in Study 4225.

# Glucose-Lowering (Pharmacodynamic) Effect By Day of Week in T1D

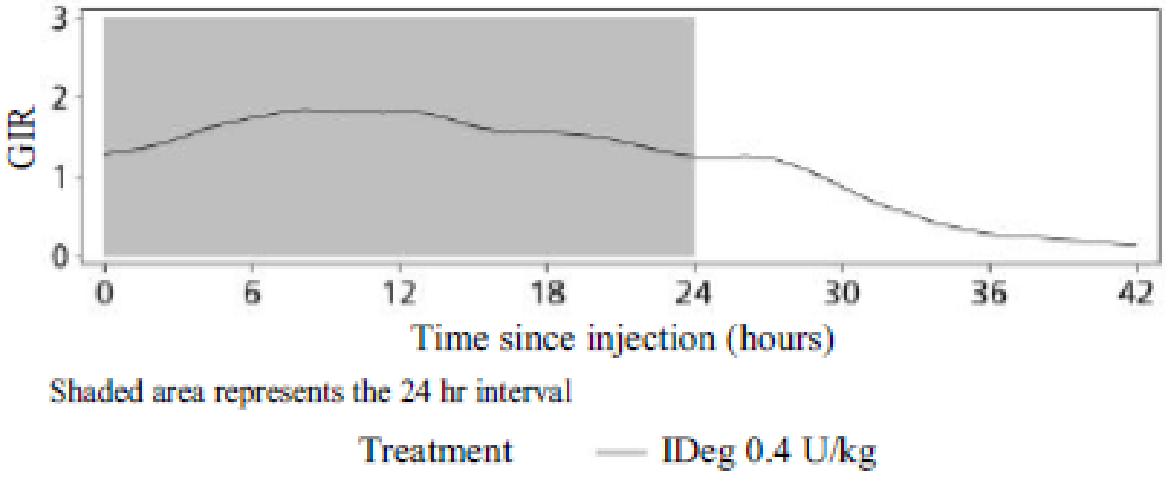
Peak glucose-lowering effect:
Days 2-4 postdose



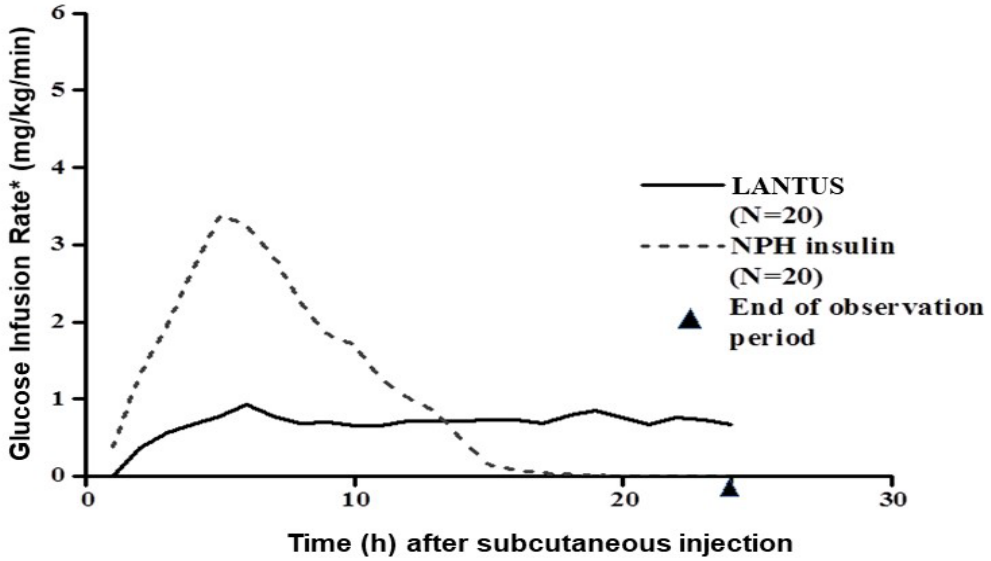

Source: FDA review

# Glucose-Lowering Profiles in T1D

## Degludec (Tresiba)




## Glargine (Lantus)




- Because these basal insulins are administered once daily, the glucose infusion rate (GIR) profile repeats throughout the week.

**Source**: Labels on Drugs@FDA, Tresiba label revised 7/2022, Lantus label revised 6/2023

# Dose Selection for T1D

- Once weekly SC injection based on weeklong half-life
- Insulin icodec dose: 7x patient's current daily basal insulin dose
- Loading dose to reach steady state faster (i.e., 2-3 wks vs 2-4 wks)

# ONWARDS 6: Study Design

Frank Pucino, PharmD, MPH
Clinical Reviewer
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

# Insulin Icodec Phase 3 Program (ONWARDS 1-6)

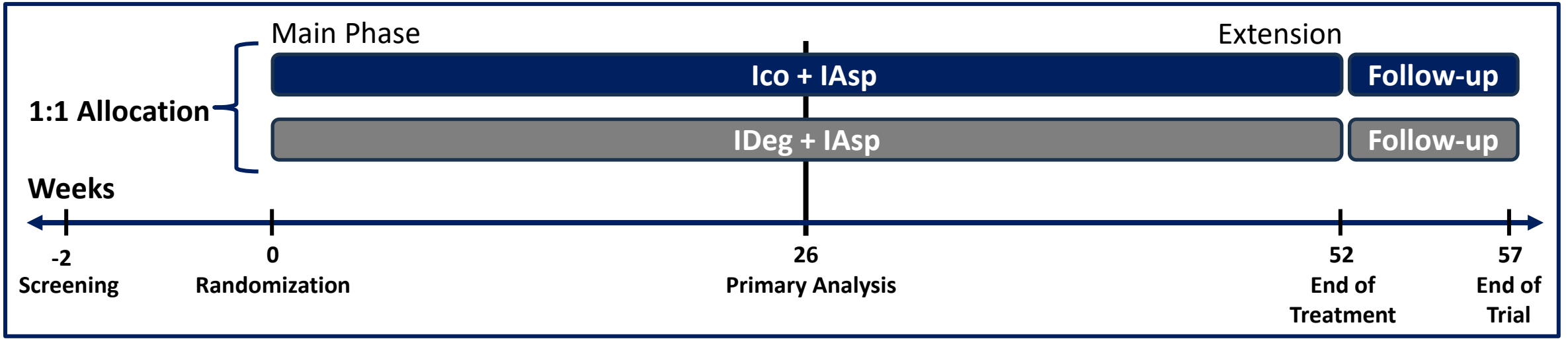
| | ONWARDS 1 | ONWARDS 2 | ONWARDS 3 | ONWARDS 4 | ONWARDS 5 | ONWARDS 6 |
|---|---|---|---|---|---|---|
| **Study Design** | Open-label | Open-label | Double-blind | Open-label | Open-label | Open-label |
| **Population** | T2D<br>Insulin naïve | T2D<br>Basal switch | T2D<br>Insulin naïve | T2D<br>Basal-bolus | T2D<br>Insulin naïve | T1D<br>Basal-bolus |
| **Insulin icodec** | Ico | Ico | Ico | Ico + IAsp | Ico + DoseGuide* | Ico + IAsp |
| **Comparator** | IGlar | IDeg | IDeg | IGlar + IAsp | Basal Ins | IDeg + IAsp |
| **Randomization** | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 |
| **Treatment Duration** | 78 (52*) wks | 26 wks | 26 wks | 26 wks | 52 wks | 52 (26¶)wks |
| **Randomized<br>Ico/Comparator** | 984<br>492/492 | 526<br>263/263 | 588<br>294/294 | 582<br>291/291 | 1085<br>542/543 | 582<br>290/292 |
| **Background Medications** | AGIs, DPP-4i, Glinides, GLP-1RA, Met, SGLT2i, SU, TZD | AGIs, DPP-4i, Glinides, GLP-1RA, Met, SGLT2i, SU, TZD | AGIs, DPP-4i, Glinides, GLP-1RA, Met, SGLT2i, SU, TZD | AGIs, DPP-4i, Glinides, GLP-1RA, Met, SGLT2i, SU, TZD | AGIs, DPP-4i, Glinides, GLP-1RA, Met, SGLT2i, SU, TZD | — |
| **HbA1c<br>Incl. Criteria** | ≥7 to ≤11% | ≥7 to ≤10% | ≥7 to ≤11% | ≥7 to ≤10% | ≥7% | ≤10% |

**Source**: Adapted from the Tabular Listing of Studies, pages 6-7.

**Abbreviations**: AGI, alpha-glucosidase inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IAsp, insulin aspart; IDeg, insulin degludec; IGlar, insulin glargine; Met, metformin; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylureas; T2D, type 2 diabetes; TZD, thiazolidinedione; and Wks, weeks. *DoseGuide App: a cloud-based system containing a titration algorithm to guidance on insulin icodec titration; ¶Duration of main part of trial.

# Study Design — ONWARDS 6

- **Design:** Phase 3, open-label, active-controlled, parallel-group, multicenter, multinational, treat-to-target (pre-breakfast self-measured plasma glucose (SMPG) 80-130 mg/dL)
- **Population:** 582 T1D patients (1:1 randomized) to insulin icodec (n=290) vs. insulin degludec (n=292)
- **Duration:** 59 wks (2-wk screening period, 26-wk main treatment period, 26-wk extension phase, and 5-wk follow-up period)




**Source**: Derived from the Clinical Study Protocol.

# Key Inclusion/Exclusion Criteria – ONWARDS 6

***Inclusion:***

- Adults (≥18 years) with T1D diagnosed and treated with MDII for ≥1 year and screening A1C <10%

***Exclusion:***

- Hypersensitivity to study medications
- Female who is pregnant or intends to become pregnant, or breastfeeding
- Cardiovascular event within 180 days
- New York Heart Association (NYHA) Class IV heart failure,
- Renal (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 $m^2$) or hepatic (alanine amino transferase [ALT] ≥2.5x upper limit of normal [ULN] or bilirubin [BILI] >1.5x ULN) impairment
- Hypoglycemic unawareness
- Recurrent severe hypoglycemic episodes within the year
- Systolic blood pressure (SBP) ≥180 mmHg or diastolic blood pressure [DBP] ≥110 mmHg
- Uncontrolled/unstable diabetic retinopathy/maculopathy
- Malignant neoplasm within 5 years

# Demographics & Clinical Characteristics

| | ONWARDS 6 | |
|---|---|---|
| | **IDeg + IAsp** | **Ico + IAsp** |
| Randomized | N=292 | N=290 |
| Age (y) — Mean (SD) | 44.2 (14.1) | 44 (14) |
| Female Sex — % | 41.1 | 43.1 |
| Race — % | | |
| White | 74.7 | 79.3 |
| Asian | 24.7 | 17.6 |
| Black/African American | 0.7 | 3.1 |
| Weight (kg) — Mean (SD) | 77.1 (16.8) | 78.6 (17.6) |
| BMI ($kg/m^2$) — Mean (SD) | 26.2 (4.5) | 26.8 (5.0) |
| DM Duration (y) — Mean (SD) | 19 (12.9) | 20 (13.2) |
| HbA1c (%) — Mean (SD) | 7.6 (0.9) | 7.6 (1) |
| eGFR ($mL/min/1.73m^2$) — Mean (SD) | 97 (19.6) | 98.5 (18.7) |

**Source**: Derived from the ISS adsl.xpt, adlb.xpt , advs.xpt datasets.
Abbreviations: IAsp, insulin aspart; Ico, insulin icodec; IDeg, insulin degludec; SD, standard deviation

# Initiation of Study Medications — ONWARDS 6

- **Insulin icodec (once weekly on the same day of the week)**

  ***First injection:***

  - Pretrial daily basal insulin dose x7, plus 50% one-time additional dose for subjects with a screening A1C <8% and a 100% one-time additional dose for subjects with a screening A1C ≥8%
  - Subjects previously receiving insulin glargine U-300 or twice daily basal insulin received a 50% one-time additional dose regardless of the screening A1C (i.e., total daily basal insulin dose before randomization x7 + 50%)

  ***Subsequent doses:***

  - Equivalent to the total daily dose x7 (rounded to nearest dose divisible by 10)

- **Insulin degludec (once daily)**
  - Switching from previous basal insulin in accordance with local labeling
- **Insulin aspart (2-4 times daily)**
  - Switching from previous bolus insulin done unit-to-unit

# Insulin Titration Algorithms

**Basal insulin:** Weekly adjustment based on lowest of 3 prebreakfast SMPG values (2 days prior and on the day of titration)

| Lowest of the SMPG values | Insulin Icodec Dose Adjustment (units/week) | Insulin Degludec Dose Adjustment (units/day) |
|---|---|---|
| >130 mg/dL | +20 | +3 |
| 80–130 mg/dL | 0 | 0 |
| <80 mg/dL | −20 | −3 |

**Bolus insulin:** Weekly adjustment based on lowest preprandial or bedtime SMPG values measured in the week before titration

| Lowest Preprandial and Bedtime SMPG | Insulin Aspart Dosage Adjustment (units) |
|---|---|
| >130 mg/dL | +1 |
| 80–130 mg/dL | 0 |
| <80 mg/dL | −1 |

**Source**: Adapted from the Clinical Study Protocol, pages 81-82.

# Glucose Monitoring

- Subjects used a Dexcom G6 CGM device for the duration of the trial
  - Low or high glucose alerts were not blinded
- Subjects received a glucose meter (Roche Accu-Chek) and measured a 4-point daily SMPG from Weeks 0 to the end of trial
  - Pre-breakfast, pre-lunch, pre-dinner, and at bedtime
  - SMPG values were transferred daily into an electronic diary (eDiary)

# ONWARDS 6: Summary of Efficacy

Roberto Crackel, PhD

Senior Mathematical Statistician

Office of Biostatistics, Division of Biometrics II

# ONWARDS 6 Trial Design and Objective

- Trial design: Randomized (1:1), 2-arm, open-label, active-controlled
- Trial duration: 26-week treatment period (main phase) with 26-week extension and 5-week follow-up period
- Primary objective: To confirm the effect on glycemic control of once weekly insulin icodec in participants with T1D, 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%

# Primary Estimand: Treatment Policy

- Treatment condition: Insulin icodec or insulin degludec, irrespective of adherence to randomized treatment and changes to anti-diabetic background medication
- Primary endpoint: Change from baseline to Week 26 in A1C (%)
- Population: Adults with T1D and ≥1 year of treatment with MDII on a basal and bolus insulin analog regimen
- Intercurrent events: Treatment discontinuation or withdrawal from the trial
  - Handling of data after intercurrent events: All available data, regardless of treatment discontinuation were used in the analysis
- Population level summary measure: Difference in mean changes from baseline in A1C at Week 26 between insulin icodec and insulin degludec

# Multiple Imputation for Handling Missing Data

- Impute missing data based on participants who discontinued randomized treatment prior to the endpoint visit and had their endpoint measurement
  - Applicant's primary analysis in the submission
- If the number of participants who were off treatment with Week 26 data is insufficient, a return-to-baseline (RTB) would be taken.
  - Participants' endpoint measurement is drawn from a normal distribution centered at the participants baseline measurement with a random error

# Data Capture of A1C at Week 26

| | Insulin Icodec | Insulin Degludec |
|---|---|---|
| **# in Full Analysis Set [N]** | 290 | 292 |
| **# with week 26 data [n(%)]** | 274 (94.5%) | 283 (96.9%) |
| **On treatment [n]** | 269 | 281 |
| **Off treatment [n]** | **5** | **2** |
| **# without week 26 data [n(%)]** | **16 (5.5%)** | **9 (3.1%)** |
| **Study discontinuation [n]** | 13 | 7 |
| **On treatment and in study [n]** | 3 | 2 |

- Full Analysis Set (FAS): All randomized participants
- Number of participants who were off treatment with Week 26 data is relatively small
  - 5 participants to represent 16 participants on insulin icodec
  - 2 participants to represent 9 participants on insulin degludec
- All results from multiple imputation using RTB will be presented in this presentation

# Primary Analysis

- 1000 multiply imputed datasets were generated
- ANCOVA model with the following fixed effects and covariates
  - Treatment (Insulin icodec; Insulin degludec)
  - Region (Asia; Europe; North America)
  - Pre-trial basal insulin (once daily; twice daily)
  - Screening A1C group (<8.0%; ≥8.0%)
  - Baseline A1C
- Rubin's rule used to synthesize analysis results from 1000 multiply imputed datasets

# Results for A1C (%) at Week 26

| | Insulin Icodec | Insulin Degludec |
|---|---|---|
| **# in Full Analysis Set (FAS) [N]** | 290 | 292 |
| **Baseline Mean (SD)** | 7.59 (0.96) | 7.63 (0.93) |
| **LS Mean change from baseline (SE) at Week 26** | -0.47 (0.04) | -0.52 (0.04) |
| **Treatment difference (Ico – IDeg) (95% CI)** | **0.06 (-0.05, 0.16)** | |
| **Percentage of participants with A1C < 7.0% at Baseline** | 31% | 28% |
| **Percentage of participants with A1C < 7.0% at Week 26[a]** | 42% | 45% |

*[a] Computed based off the average number across multiply imputed datasets*
*Abbreviations: FAS, full analysis set; SE, standard error; Ico, insulin icodec; Ideg, insulin degludec*
*Source: FDA statistical reviewer*

- Noninferiority of insulin icodec is demonstrated since the upper bound of the 95% confidence interval is less than 0.3% (noninferiority margin) (p-value for noninferiority < 0.0001)
- Two-way tipping point analysis showed unlikely but not clinically impossible scenarios where the conclusion tips from noninferior to inferior
- Subgroup results are consistent with the overall population

# Secondary Efficacy Endpoints

- Change from baseline to Week 52 in A1C (%)
- Change from baseline to Weeks 26 and 52 in FPG (mg/dL)
- Time in range (70 – 180 mg/dL; %) during Weeks 22-26 and 48-52
- Change from baseline to Weeks 26 and 52 in Diabetes Treatment Satisfaction Questionnaire Status (DTSQs) Treatment Satisfaction scores

**Secondary endpoints are not adjusted for multiplicity**

# Analysis Methods

- Treatment policy estimand
- Handling of missing data
  - A1C, fasting plasma glucose (FPG), and DTSQstatus: return-to-baseline
  - Time in range (TIR): Imputed from a normal distribution centered at the average time in range for participants on insulin degludec who completed treatment with a random error
- Multiple imputation:
  - 1000 datasets; analysis of covariance (ANCOVA) (analysis of variance [ANOVA] for TIR) used to analyze each dataset; Rubin's rule

# Change in A1C (%) at Week 52

| | Insulin Icodec | Insulin Degludec |
|---|---|---|
| **# in Full Analysis Set (FAS) [N]** | 290 | 292 |
| **LS Mean change from baseline (SE) at Week 52** | -0.38 (0.04) | -0.52 (0.04) |
| **Treatment difference (Ico – IDeg) (95% CI)** | **0.14 (0.02, 0.25)** | |
| **Percentage of participants with A1C <7.0% at Week 52[a]** | 40% | 40% |

a Computed based on the average number across multiply imputed datasets
Abbreviations: FAS, full analysis set; SE, standard error; Ideg, insulin degludec

*Source: FDA statistical reviewer*

- Reduction in A1C from baseline observed in both groups
- The estimated treatment difference is nominally in favor of insulin degludec since the lower bound of the 95% CI is greater than 0

# Results for Secondary Efficacy Endpoints

| | Insulin Icodec | Insulin Degludec | Treatment Difference (Ico – IDeg) (95% CI) |
|---|---|---|---|
| **FPG (mg/dL)[1]** | **LS Mean Change From Baseline (SE)** | | |
| at Week 26 | -15.08 (3.65) | -33.66 (3.55) | 18.58 (8.58, 28.58) |
| at Week 52 | -10.46 (3.74) | -33.81 (3.62) | 23.35 (13.11, 33.59) |
| **DTSQs Treatment Satisfaction score** | | | |
| at Week 26 | 1.97 (0.27) | 3.06 (0.27) | -1.09 (-1.85, -0.34) |
| at Week 52 | 1.41 (0.33) | 3.00 (0.33) | -1.59 (-2.51, -0.67) |
| **TIR (70-180 mg/dL) (%)** | **LS Mean (SE)** | | |
| at Week 22-26 | 59.06 (0.86) | 61.06 (0.85) | -2.00 (-4.38, 0.38) |
| at Week 48-52 | 57.40 (0.91) | 59.82 (0.88) | -2.42 (-4.90, 0.07) |

*[1]FPG samples were taken before administration of insulin icodec or insulin degludec, and insulin aspart*
*Source: FDA statistical reviewer*

- Nominally favored insulin degludec in FPG and DTSQs Treatment Satisfaction score
- No difference in TIR

# Summary of Efficacy

- ONWARDS 6 demonstrated noninferiority of insulin icodec to insulin degludec, both in combination with insulin aspart in treating participants with T1DM at Week 26
- Change in 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

# ONWARDS 6: Safety Review

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# Safety Findings — ONWARDS 6

**No meaningful imbalances in:**

- Deaths
- Discontinuations due to adverse events (AEs)
- Common AEs (per labeling of other basal insulin products)
  - Edema, hypersensitivity reactions, hypokalemia, injection site reactions, lipodystrophy, pruritus, rash, and weight gain
- Serious AEs (SAEs), excluding hypoglycemia

# Hypoglycemia Risk in T1D

- Hypoglycemia is a known and accepted complication of all insulins
- Hypoglycemic episodes in T1D patients are frequent, occurring both during the day and at night, and can result in significant adverse events including death
- Clinical treatment goals seek to improve glycemic control, while minimizing hypoglycemia
- Newer insulin analog products with flatter pharmacodynamic (PD) profiles/longer half-lives may have less hypoglycemia[1-8]
  - Insulin degludec has a labeling claim for less hypoglycemia than insulin glargine[9]


1. Lane W, et al. JAMA 2017;318:33-44.
2. Home PD, et al. Diabetes Care 2015;38:2217-25.
3. Black JE, et al. Diabetes Ther 2023;14:1299-317.
4. Ratner RE, et al. Diabetes Obes Metab 2013;15:175-84.
5. Matsuhisa M, et al. Diabetes Obes Metab 2016;18:375-83.
6. Bergenstal RM, et al. Diabetes Care 2017;40:554-60.
7. Wysham C, et al. JAMA 2017;318:45-56.
8. Marso SP, et al. N Engl J Med 2017;377:723-32.
9. Tresiba [package insert]. 2022 Jul 1, available from:Drugs@FDA: FDA-Approved Drugs

# Capture / Classification of Hypoglycemia

- Events of hypoglycemia were assessed throughout the study (Day 1 through Wk 57) and defined according to the following 3 categories (consistent with American Diabetes Association [ADA] criteria[1] and FDA draft guidance[2]):
  - **Level 1 hypoglycemia:** blood glucose (BG) <70 mg/dL and ≥54 mg/dL
  - **Level 2 (clinically significant) hypoglycemia:** BG <54 mg/dL
  - **Level 3 (severe) hypoglycemia:** Severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions
- Nocturnal hypoglycemia was defined as episodes occurring between 00:01 and 05:59
- Per protocol, hypoglycemia events were captured by blood glucose meter
  - Episodes identified by CGM were to be confirmed by SMPG

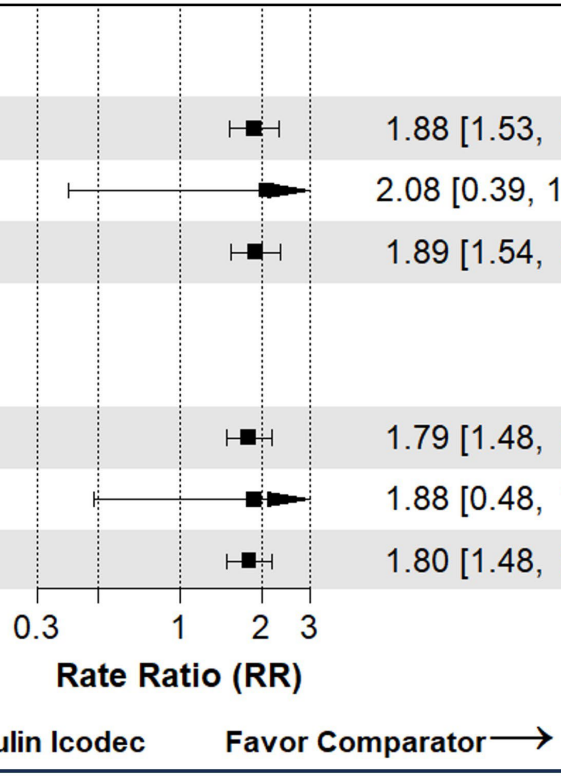
[1] American Diabetes Association Professional Practice Committee. Diabetes Care 2024;47:S111-S25.

[2] Guidance for Industry. Diabetes mellitus: efficacy endpoints for clinical trials investigating antidiabetic drugs and biological products. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

# Higher Level 2 or 3 Hypoglycemia Event Rates (SMPG)

## Overall Hypoglycemic Episode (Level 2, Level 3) Capture: SMPG

| | Insulin Icodec (N = 290) | | | | Insulin Degludec (N = 292) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | E | PY | Rate | n | E | PY | Rate | RR [95% CI] | RD [95% CI] |
| *Main (Weeks 0-26)* | | | | | | | | | | |
| Level 2 | 246 | 2789 | 142.3 | 1959.8 | 223 | 1478 | 144.1 | 1025.5 | 1.88 [1.53, 2.32] | 9.34 [8.45, 10.24] |
| Level 3 | 9 | 47 | 142.3 | 33.0 | 9 | 17 | 144.1 | 11.8 | 2.08 [0.39, 10.96] | 0.21 [0.10, 0.32] |
| Level 2 or Level 3 | 247 | 2836 | 142.3 | 1992.8 | 223 | 1495 | 144.1 | 1037.3 | 1.89 [1.54, 2.33] | 9.56 [8.65, 10.46] |
| *Main + Extension (Weeks 0-57)* | | | | | | | | | | |
| Level 2 | 262 | 5047 | 300.2 | 1681.4 | 250 | 2811 | 309.6 | 908.0 | 1.79 [1.48, 2.18] | 7.73 [7.16, 8.31] |
| Level 3 | 13 | 56 | 300.2 | 18.7 | 12 | 25 | 309.6 | 8.1 | 1.88 [0.48, 7.36] | 0.11 [0.05, 0.16] |
| Level 2 or Level 3 | 263 | 5103 | 300.2 | 1700.1 | 250 | 2836 | 309.6 | 916.1 | 1.80 [1.48, 2.18] | 7.83 [7.26, 8.41] |

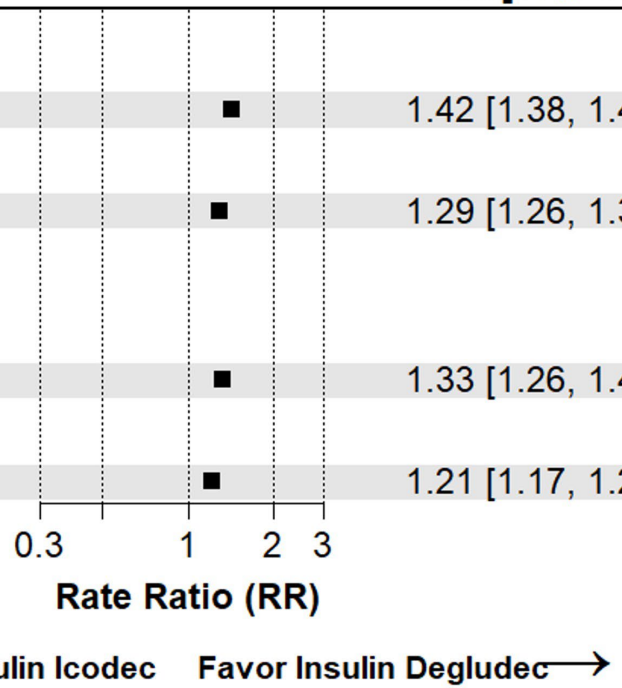



**Source**: FDA safety statistical reviewer. ONWARDS 6 clinical trial data, adsl.xpt, adhypoen.xpt, April 6, 2023 (sequence #0001), August 2, 2023 (sequence #0010).
**Analysis**: RR and the 95% CI estimated using a negative binomial regression model with treatment, region, A1C group at screening and pre-trial basal insulin treatment as fixed factors, and the logarithm of the time period for which the events are considered as an offset. Rate difference (RD) notes additional number of events per person year. 95%CI for RD computed using normal approximation. FAS, all subjects randomized.
**Abbreviations**: E, number of events; N, number of subjects; PY, patient years; Rate (number of events per 100 PY); RR, rate ratio; RD, rate difference; CI, confidence interval; SMPG, self-measured plasma glucose.

# Higher Level 2 Hypoglycemia Event Rates (CGM)

## Hypoglycemic Episode Capture (Level 2): CGM

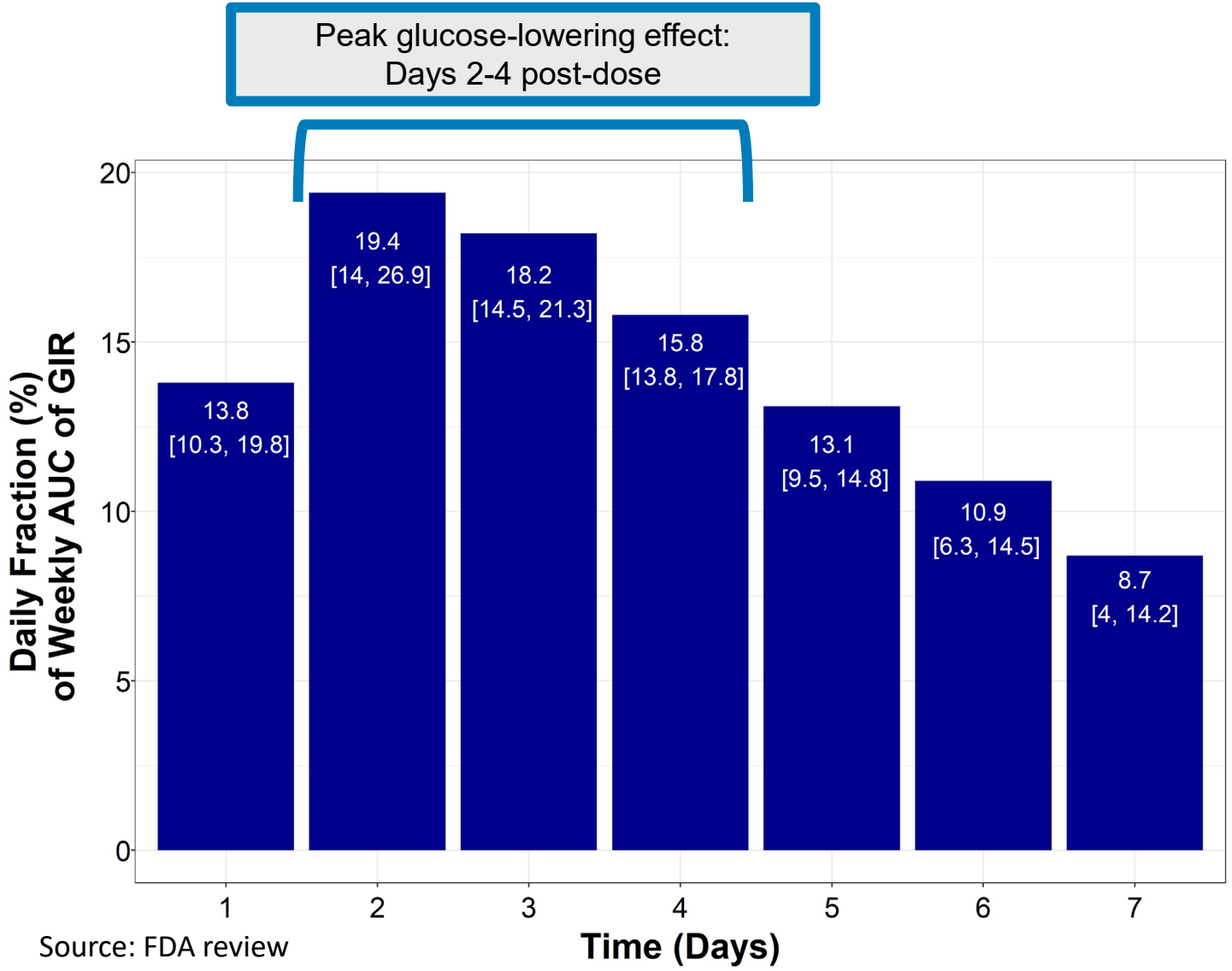
| | Insulin Icodec (N = 290) | | | | Insulin Degludec (N = 292) | | | | RR [95% CI] | RD [95% CI] |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | E | PY | Rate | n | E | PY | Rate | | |
| Total | | | | | | | | | | |
| *Main (26 Weeks)* | | | | | | | | | | |
| Level 2 | 288 | 13883 | 142.3 | 9756.1 | 284 | 9965 | 144.1 | 6915.3 | 1.42 [1.38, 1.45] | 28.40 [26.29, 30.52] |
| *Extension (57 Weeks)* | | | | | | | | | | |
| Level 2 | 289 | 26986 | 300.2 | 8989.3 | 287 | 21623 | 309.6 | 6984.2 | 1.29 [1.26, 1.31] | 20.05 [18.63, 21.47] |
| Nocturnal | | | | | | | | | | |
| *Main (26 Weeks)* | | | | | | | | | | |
| Level 2 | 261 | 2790 | 142.3 | 1960.6 | 245 | 2135 | 144.1 | 1481.6 | 1.33 [1.26, 1.40] | 4.79 [3.83, 5.75] |
| *Extension (57 Weeks)* | | | | | | | | | | |
| Level 2 | 272 | 5818 | 300.2 | 1938.0 | 267 | 4954 | 309.6 | 1600.1 | 1.21 [1.17, 1.26] | 3.38 [ 2.71, 4.05] |




**Source**: FDA safety statistical reviewer. ONWARDS 6 clinical trial data, adsl.xpt, adcgm.xpt, adcgmen.xpt, January 8, 2024 (sequence #0037).
**Abbreviations**: E, number of events; N, number of subjects; PY, patient years of exposure; Rate (number of events per 100 PY); RR, rate ratio; RD, rate difference; CI, confidence interval; CGM, continuous glucose monitoring
**Analysis**: Descriptive analysis to assess the robustness of the conclusions from the pre-specified negative binomial model analysis of hypoglycemic episodes captured using SMPG. Therefore, crude RR and 95% confidence intervals were computed. The crude RR was not adjusted for any covariates. Rate difference (RD) notes additional number of events per person year. 95%CI for RD computed using normal approximation

# Higher Glucose-Lowering Effect on Days 2 to 4

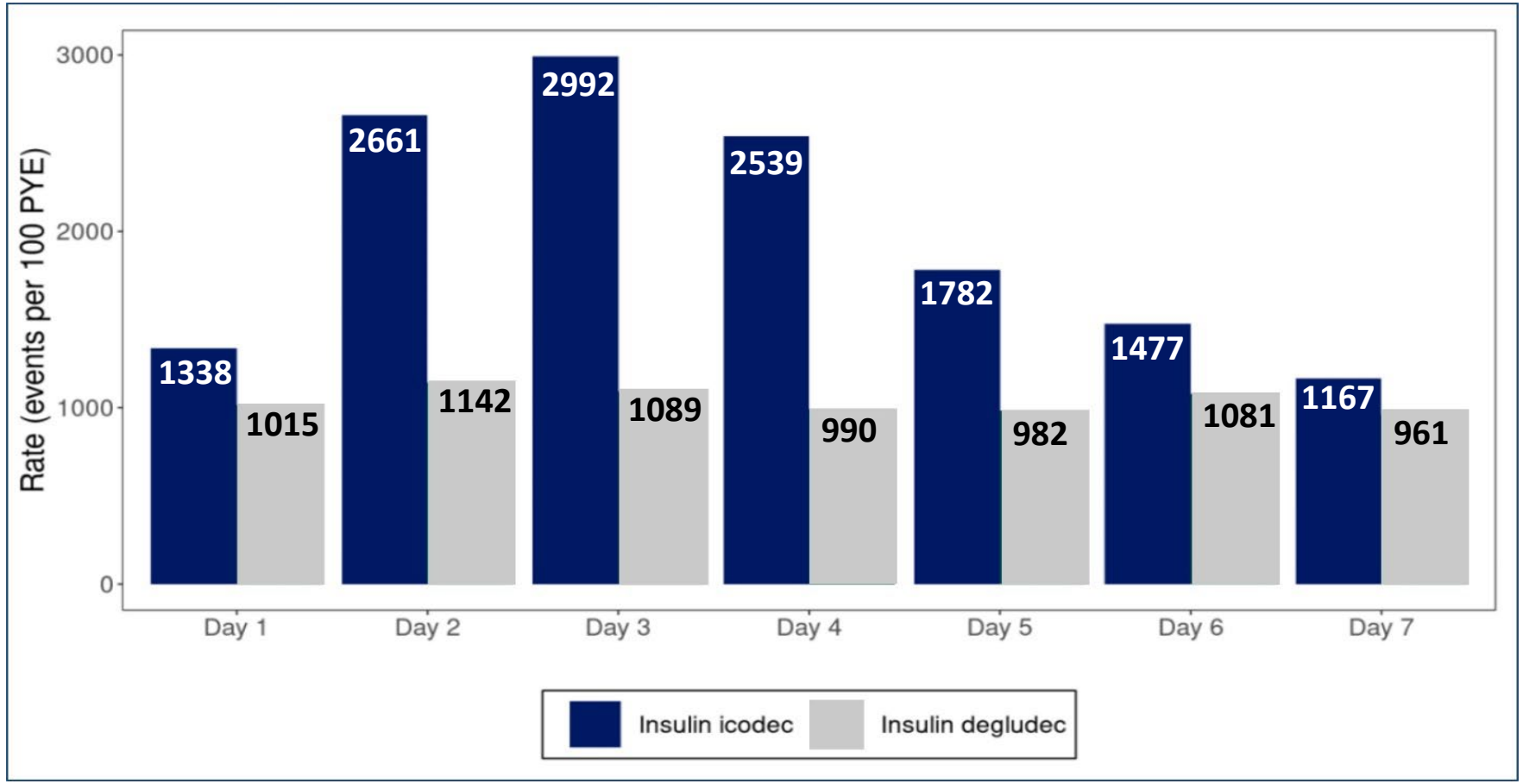
## Glucose-Lowering (Pharmacodynamic) Effect By Day of Week in T1D




Source: FDA review

# Higher Rate of Level 2 or 3 Hypoglycemia on Days 2 to 4

## Event Rate of Level 2 or 3 Hypoglycemia (SMPG) by Treatment Day

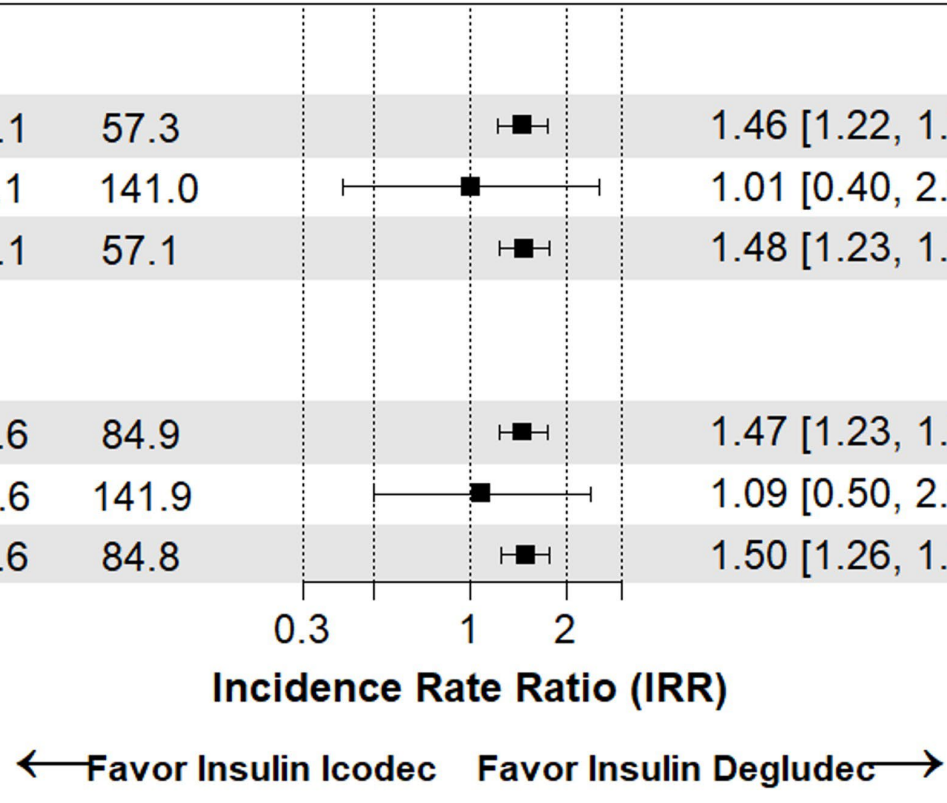



**Source**: FDA safety statistical reviewer. ONWARDS 6 clinical trial data, adsl.xpt, adhypoen.xpt, April 6, 2023 (sequence #0001).
**Abbreviations**: PY, patient years of exposure (1 PY = 365.25 days); SMPG, self-measured plasma glucose.
Observed data from the safety analysis set (SAS) for the main 26-week treatment period.

# Higher Incidence of Level 2 or 3 Hypoglycemia

## Incidence Rate of Level 2 or 3 Hypoglycemia (SMPG)

| | Insulin Icodec (N = 290) | | | Insulin Degludec (N = 292) | | | |
|---|---|---|---|---|---|---|---|
| | n | PY | Time At Risk | n | PY | Time At Risk | IRR [95% CI] |
| *Main (Weeks 0-26)* | | | | | | | |
| Level 2 | 246 | 142.3 | 43.3 | 223 | 144.1 | 57.3 | 1.46 [1.22, 1.75] |
| Level 3 | 9 | 142.3 | 139.7 | 9 | 144.1 | 141.0 | 1.01 [0.40, 2.54] |
| Level 2 or Level 3 | 247 | 142.3 | 42.8 | 223 | 144.1 | 57.1 | 1.48 [1.23, 1.77] |
| *Main + Extension (Weeks 0-57)* | | | | | | | |
| Level 2 | 262 | 300.2 | 60.6 | 250 | 309.6 | 84.9 | 1.47 [1.23, 1.75] |
| Level 3 | 13 | 300.2 | 141.1 | 12 | 309.6 | 141.9 | 1.09 [0.50, 2.39] |
| Level 2 or Level 3 | 263 | 300.2 | 59.5 | 250 | 309.6 | 84.8 | 1.50 [1.26, 1.78] |




**Source**: FDA safety statistical reviewer. ONWARDS 6 clinical trial data, adsl.xpt, adhypoen.xpt, April 6, 2023 (sequence #0001), August 2, 2023 (sequence #0010).
**Abbreviations**: N, number of subjects; PY, patient years of exposure; IRR, incidence rate ratio; SMPG, self-measured plasma glucose.
Incidence rate (IR) was defined as the number of subjects with at least one hypoglycemic episode divided by the time at risk. For subjects who experienced at least one event, time at risk was defined as the time from the first drug exposure to the first event. For subjects who did not experience an event, time at risk was set to equal the on-treatment period. IRR was not adjusted for covariates.

# No Difference in the Duration of Level 2 Hypoglycemia

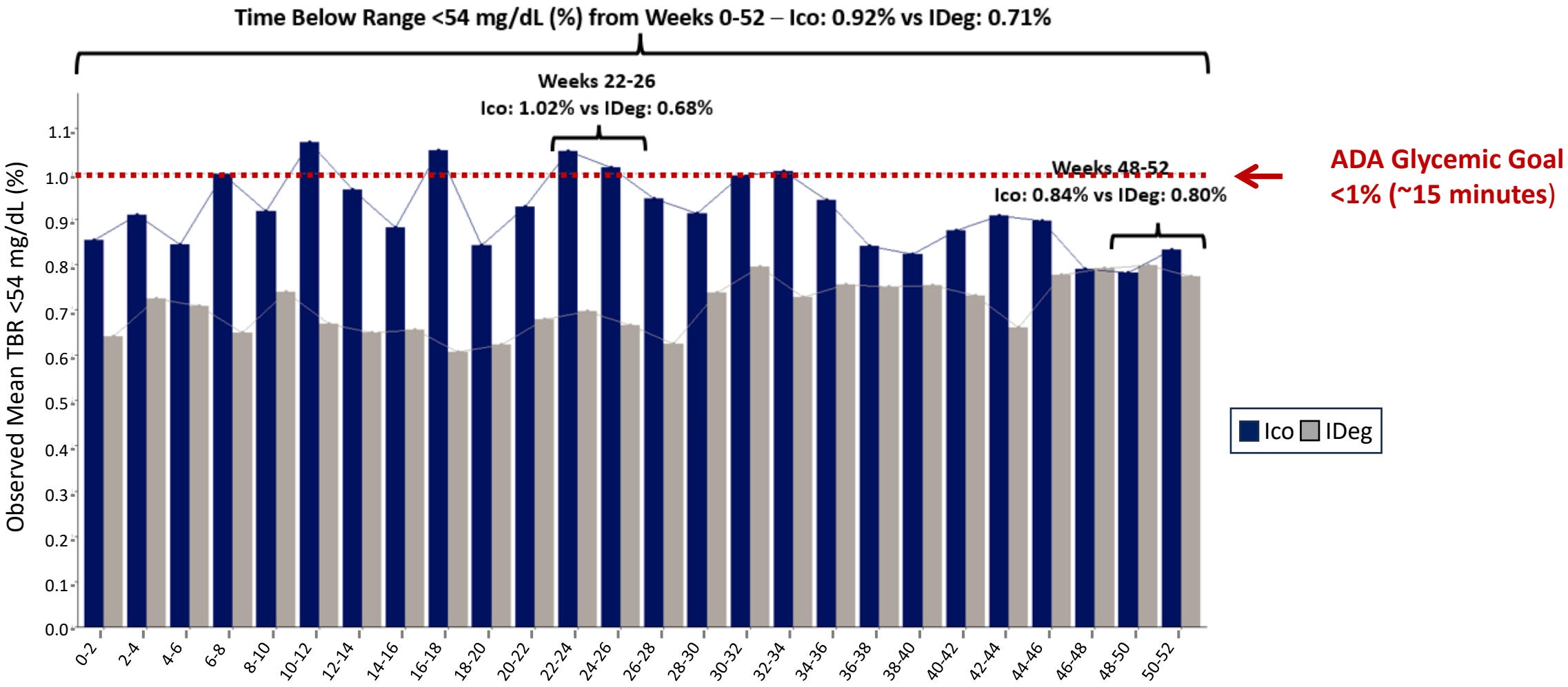
## Duration of Level 2 Hypoglycemic Episodes (CGM)*

| Variable | Ico | IDeg |
|---|---|---|
| Total number of Level 2 events – N | 29,152 | 23,344 |
| **Mean (SD) duration – mins** | **40.2 (41.8)** | **41.3 (45.6)** |
| Minimum; Maximum – mins | 15; 730 | 15; 1225 |
| **Median (IQR) duration – mins** | **25 (20, 45)** | **25 (20, 45)** |

**Source**: Statistical analyst. Data (adcgmen.xpt, adsl.xpt) in the Applicant's Regulatory Response, April 8, 2024 (sequence #0061).

*Duration of level 2 hypoglycemia defined as the time from an interstitial glucose value <54 mg/dL for at least 15 minutes to when it was ≥54 mg/dL for at least 15 minutes.
**Abbreviations**: CGM, continuous glucose monitoring; E, number of events; Ico: insulin icodec; IDeg; insulin degludec; min, minutes; TBR, time below range

# Time Below Range <54 mg/dL Is Higher With Insulin Icodec




**Source**: Statistical analyst. sv.xpt, mdvisit.xpt, and mdparam.xpt (sequence #0010), adsl.xpt (sequence #0001), adcgm.xpt (sequence #0055).
**Abbreviations**: FAS, full analysis set; Ico, insulin icodec, IDeg, insulin degludec; TBR, time below range

# Serious Adverse Events

- Serious Adverse Events (SAEs) defined as:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of hospitalization
  - Results in persistent or significant disability/incapacity
  - Is a congenital anomaly/birth defect
  - Important medical event
- Hypoglycemic episodes fulfilling criteria for an SAE were documented:
  - eDiary, eCRF AE, and safety information form

# More Serious Adverse Events of Hypoglycemia

## Insulin icodec

- 9 (3%) subjects experienced 14 SAEs (4.66 events/100 patient-years [PY])
  - Dose reduced (n=5 events)
  - IV glucose administered (n=4 events)
  - Glucagon administered (n=2 events)

## Insulin degludec

- 3 (1%) subjects experienced 3 SAEs (1 event/100 PY)
  - Dose not changed (n=1 event)
  - Dose reduced (n=1 event)
  - Drug interrupted (n=1 event)

**None of the SAEs resulted in treatment discontinuation or study withdrawal in either study group**



**Source**: Clinical Trial Report, pages 379-387.

# Applicant Proposed Labeling to Mitigate Hypoglycemia Risk

- Restrict use to T1D patients wearing a CGM device with %CV ≤36% prior to initiation of insulin icodec and without a history of recurrent severe hypoglycemia or hypoglycemia unawareness
- Discontinue the product in patients who experience recurring hypoglycemic events
- Inform patients and providers that the maximal glucose-lowering effect of insulin icodec occurs during days 2-4 after each weekly injection
  - Consider reducing the bolus insulin dose between days 2 and 4 after each weekly insulin icodec injection

# Exploratory Analysis of %CV Subgroup

Jaejoon Song, PhD

Senior Statistical Reviewer

Division of Biometrics VII

# Glycemic Variability

- Percent coefficient of variation (%CV): measure of glucose variability
  - Calculated as 100 × (standard deviation [SD] divided by mean glucose)
- Glycemic variability target threshold in T1D: %CV ≤36%
  - Lower risk of hypoglycemia
  - Discussed by the American Diabetes Association (ADA) and International Consensus, and supported by medical literature
  - Identified by the Applicant from exploratory analyses of patient characteristics, including known risk factors for hypoglycemia

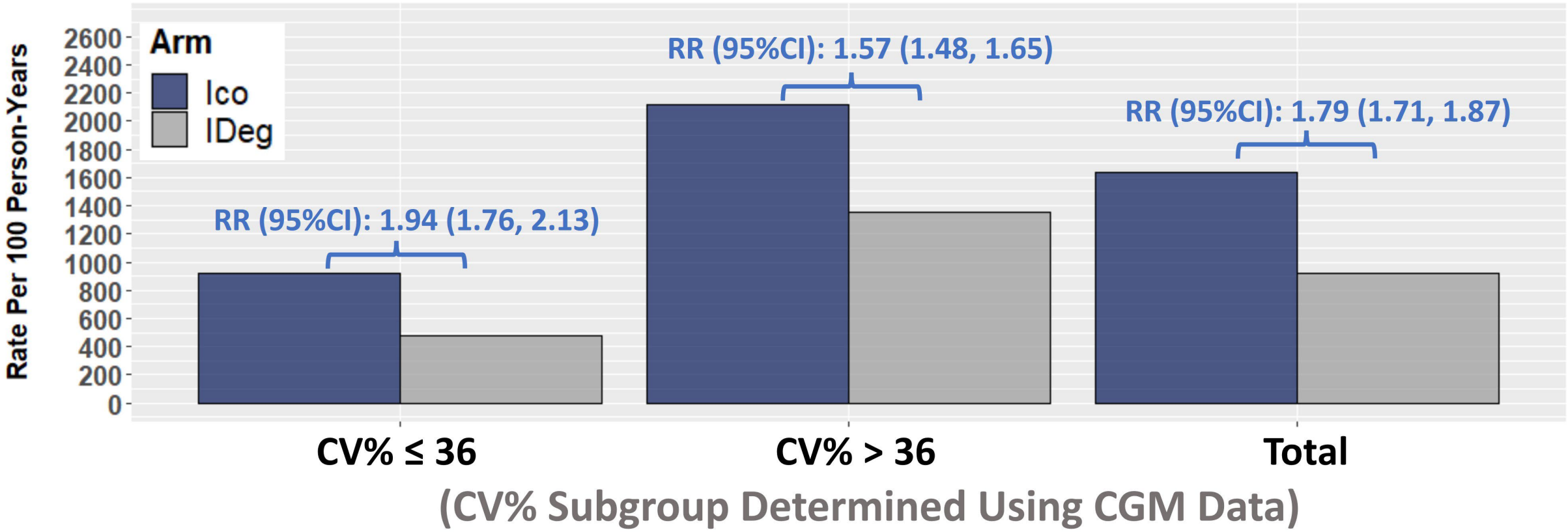
American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S111-S25.

Battelino T, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. Lancet Diabetes Endocrinol. 2023;11(1):42-57.

# Exploratory Analysis of %CV Subgroup

- Subgroup defined using %CV at Week 0-2 after treatment initiation (based on CGM)
- Considered data for subjects with ≥70% of planned CGM
- Rate of Level 2/3 hypoglycemic episodes by %CV subgroup
  - Crude rate ratio (without adjustment of any covariates) to assess arm differences within subgroups
    - 95% CI using normal approximation
- Distribution of %CV to examine stability over 52-week study period

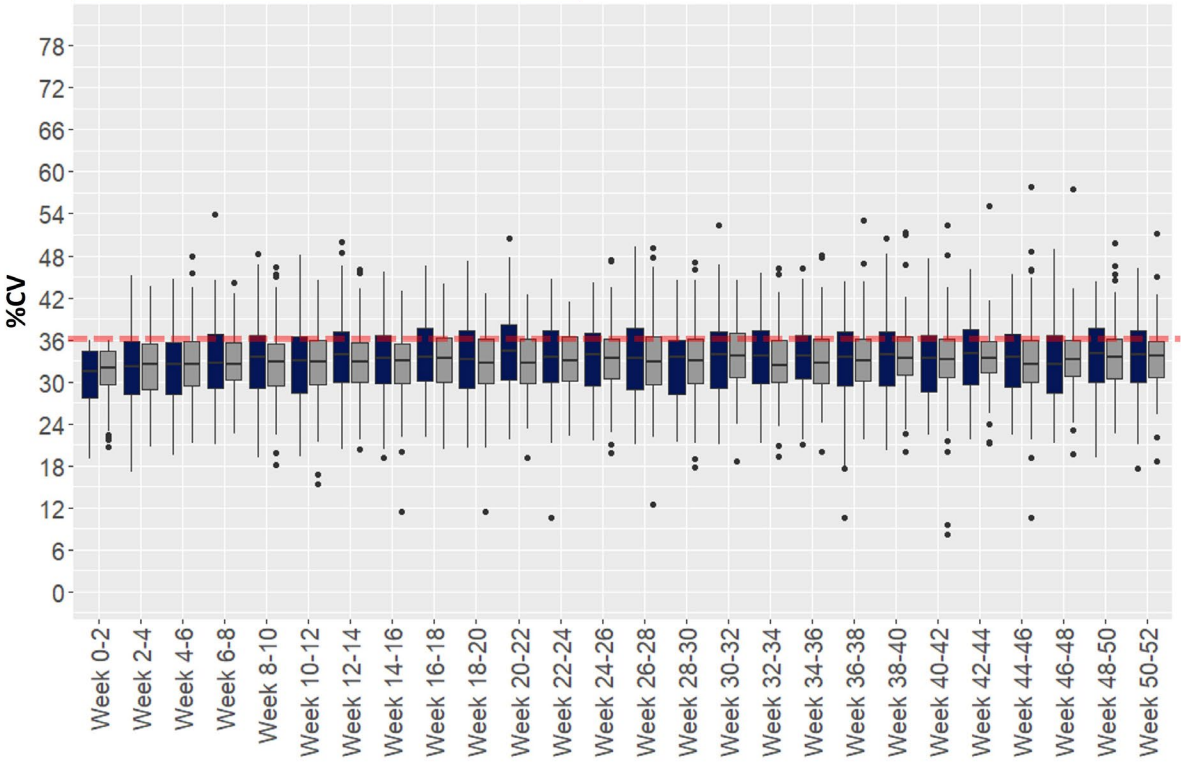
# Level 2 or 3 Hypoglycemic Episode (SMPG) by %CV Weeks 0-57 (Main + Extension)



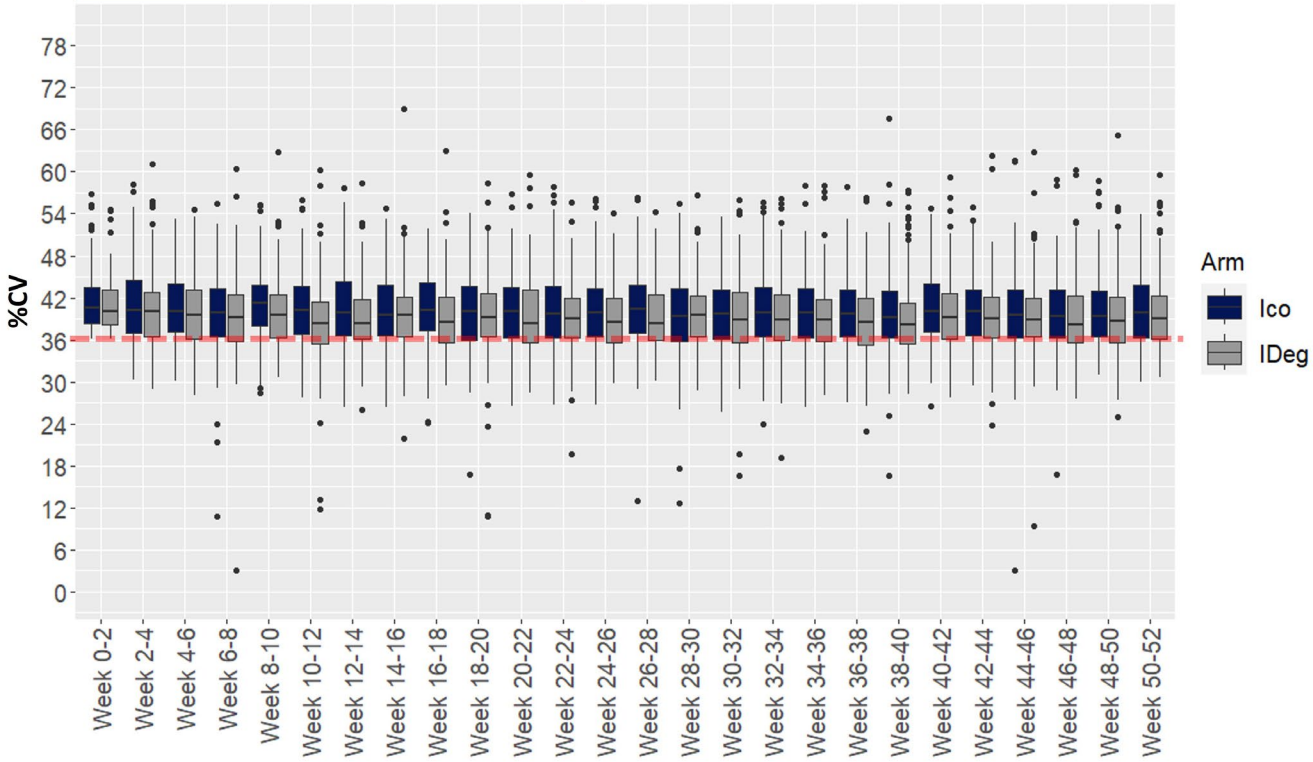

**Source:** Data (adcgmen2.xpt, adsl.xpt) in the Applicant's Regulatory Response, February 8, 2024 (sequence #0042).
**Note:** RR was crude rate ratio, and 95% CI were calculated using normal approximation. Considered data for subjects with at least 70% of CGM measurements over Wks 0-2.
**Abbreviations**: n, number of subjects with one or more level 2 or level 3 hypoglycemic episode; CV, coefficient of variation; E, number of hypoglycemic episodes

# %CV Appears Generally Stable Over 52 Weeks

**Subjects With %CV ≤ 36 at Weeks 0-2**




**Subjects With %CV > 36 at Weeks 0-2**




**Source:** Data (adcgmen2.xpt, adsl.xpt) in Applicant's Regulatory Response, February 8, 2024 (sequence #0042).
**Note: D**istribution of %CV was determined based on CGM data.
**Abbreviations**: CV, coefficient of variation; Ins Deg, insulin degludec; Ins Ico, insulin icodec.

# Summary of Exploratory %CV Subgroup Analyses

- Numerically lower rates of level 2 or level 3 hypoglycemia observed in subjects with %CV ≤ 36 compared to those with %CV > 36, in both arms
  - Within %CV subgroup (%CV ≤ 36 or %CV > 36), rate of level 2 or level 3 hypoglycemia episodes still numerically higher in the insulin icodec arm compared to the insulin degludec arm
- %CV after treatment initiation appeared to be generally stable over 52-weeks

# Limitations of Exploratory %CV Subgroup Analyses

- Subgroup defined on post-randomization variable
  - %CV based on CGM in the first 2 weeks after treatment initiation
- Choice of subgroup was post hoc
- Different variable (***pre-treatment CV%***) used to define the Applicant-proposed indication
  - Applicant's assumption: pre-treatment %CV levels comparable to %CV levels after treatment initiation
  - Data to confirm this assumption not provided

# Pharmacometric Modeling of Alternative Dose Titration Strategies

Elyes Dahmane, PhD

Pharmacometrics Reviewer

Office of Clinical Pharmacology

# Can Alternative Dose Titration Schedules Reduce Level 2 Hypoglycemia and Maintain Glycemic Control?

- Titration schedule for insulin icodec in study ONWARDS 6:
  - Up-titration: if **lowest** (SMPG of **days 5 to 7)** > 130 mg/dL
  - Down-titration: if **lowest** (SMPG of **days 5 to 7)** < 80 mg/dL

* SMPG: Self measured pre-breakfast fasting plasma glucose

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- Question:
  - Does **dose titration of** insulin **icodec** based on **lowest SMPG** of **alternative days** (e.g., **days 2-4** or **days 3-5**) reduce the incidence of level 2 hypoglycemic event and maintain acceptable efficacy?

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- Question:
  - Does **dose titration of** insulin **icodec** based on **lowest SMPG** of **alternative days** (e.g., **days 2-4** or **days 3-5**) reduce the incidence of level 2 hypoglycemic event and maintain acceptable efficacy?
- Analysis: Dose-response and Exposure-response model simulations of following scenarios:
  - Dose titration of insulin **icodec** based on **lowest SMPG** of **days 2-4**
  - Dose titration of insulin **icodec** based on **lowest SMPG** of **days 3-5**
  - Reduce dose of **bolus insulin (insulin aspart) on days 2-4** and titrate insulin icodec per protocol (i.e., lowest SMPG of days 5 to 7)

* SMPG: Self measured pre-breakfast fasting plasma glucose

# Applicant's Results From Modeling Alternative Titration Schedules

| Titration Scenarios | Week 26 FPG (mg/dL) | Week 26 A1C(%) | Change From Baseline in A1C (%) | Cumulative Level 2 Hypoglycemia (PYE) |
|---|---|---|---|---|
| **Observed data** (ONWARDS 6) | 160 (154 - 167) | 7.15 (7.01 - 7.29) | -0.47 (-0.6 ; -0.33) | 19.93 |

Values are means and 95%CI

[a] GMI (glucose management indicator), calculated from the model-predicted CGM data, is used as a surrogate for A1C.

Lowest FPG Days 5-7 (per protocol)**:** per Study 4625 (ONWARDS 6) protocol titration based on **lowest SMPG of last 3 days of the week**.

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| **Model prediction based on:** | | | | |
| ❖ Lowest SMPG Days 5-7 (per protocol) | 154 (152 - 157) | 7.20 (7.16 - 7.25) [a] | -0.43 (-0.47 ; -0.38) [a] | 21.22 (19.32 - 23.56) |

Values are means and 95%CI

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| ❖ **Lowest SMPG of Days 2-4** | **186 (183 - 189)** | **7.76 (7.69 - 7.83)** [a] | 0.13 (0.06 ; 0.20) [a] | **14.67 (13.25 - 16.74)** |
| ❖ **Lowest SMPG of Days 3-5** | **178 (175 - 181)** | **7.63 (7.57 - 7.70)** [a] | -0.00 (-0.06 ; 0.07) [a] | **15.47 (13.98 – 17.92)** |

Values are means and 95%CI

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Lowest FPG Days 5-7 (per protocol)**:** per Study 4625 (ONWARDS 6) protocol titration based on **lowest SMPG of last 3 days of the week**.

# Applicant's Results From Modeling Alternative Titration Schedules

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| **Model prediction based on:** | | | | |
| ❖ Lowest SMPG Days 5-7 (per protocol) | 154 (152 - 157) | 7.20 (7.16 - 7.25) [a] | -0.43 (-0.47 ; -0.38) [a] | 21.22 (19.32 - 23.56) |
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Values are means and 95%CI

[a] GMI (glucose management indicator), calculated from the model-predicted CGM data, is used as a surrogate for A1C.

Lowest FPG Days 5-7 (per protocol)**:** per Study 4625 (ONWARDS 6) protocol titration based on **lowest SMPG of last 3 days of the week**.

# Applicant's Results From Modeling Alternative Titration Schedules

| Titration Scenarios | Week 26 FPG (mg/dL) | Week 26 A1C(%) | Change From Baseline in A1C (%) | Cumulative Level 2 Hypoglycemia (PYE) |
|---|---|---|---|---|
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| **Model prediction based on:** | | | | |
| ❖ Lowest SMPG Days 5-7 (per protocol) | 154 (152 - 157) | 7.20 (7.16 - 7.25) [a] | -0.43 (-0.47 ; -0.38) [a] | 21.22 (19.32 - 23.56) |
| ❖ **Lowest SMPG of Days 2-4** | **186 (183 - 189)** | **7.76 (7.69 - 7.83)** [a] | 0.13 (0.06 ; 0.20) [a] | **14.67 (13.25 - 16.74)** |
| ❖ **Lowest SMPG of Days 3-5** | **178 (175 - 181)** | **7.63 (7.57 - 7.70)** [a] | -0.00 (-0.06 ; 0.07) [a] | **15.47 (13.98 - 17.92)** |
| ❖ Per-protocol for Icodec (Days 5-7) + **30% dose reduction** of **bolus insulin** on Days 2-4 | **155 (152 - 157)** | **7.26 (7.21 - 7.31)** [a] | -0.37 (-0.42 ; -0.32) [a] | **12.76 (11.45 - 14.41)** |

[a] GMI (glucose management indicator), calculated from the model-predicted CGM data, is used as a surrogate for A1C.

Lowest FPG Days 5-7 (per protocol): per Study 4625 (ONWARDS 6) protocol titration based on **lowest SMPG of last 3 days of the week**.

# Conclusions From Exposure-Response Modeling

- Modeling predicts that the alternative titration schedules considered for insulin icodec lower risk of hypoglycemia but compromise glycemic control.
- Modeling predicts a 30% reduction of bolus insulin dose on days 2-4 of each weekly insulin icodec dose may reduce the risk of hypoglycemia and maintain glycemic control.

# ONWARDS 6: Benefit-Risk Summary

Frank Pucino, Pharm D, MPH

Clinical Reviewer

Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

# Summary of Efficacy Results

- Insulin icodec was determined to be noninferior to insulin degludec at Week 26 in ONWARDS 6
  - Would decrease the number of basal insulin injections from 7 to 1 per week
- Results of the secondary endpoints related to glycemic efficacy 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

# Summary of Safety

- No imbalances in deaths, SAEs (excluding hypoglycemia), or discontinuations due to AEs
- At Week 57, insulin icodec had 50% higher incidence rate and 80% higher event rate of hypoglycemia
  - Higher rates were observed regardless of whether hypoglycemia was captured by SMPG or CGM
  - Risk greatest on Days 2-4 following each weekly injections
  - Time below range (TBR) <54 mg/dL higher in the insulin icodec arm
- Hypoglycemic events similar in duration, management and recovery between arms

# Summary of Hypoglycemia Mitigation Strategies

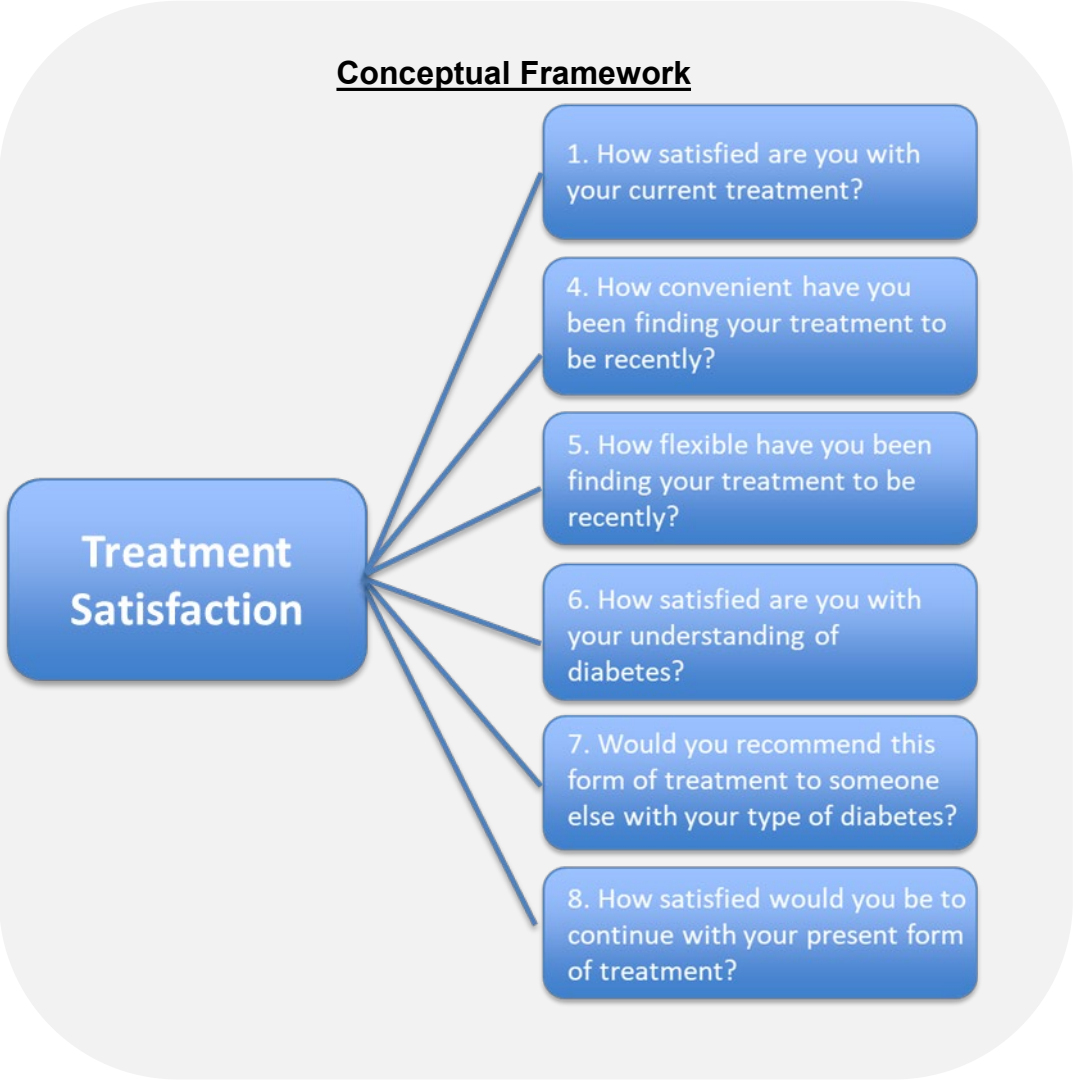
- Exploratory analyses assessed whether patient selection could mitigate the risk of hypoglycemia
  - Selecting patients with a CV ≤36% could potentially reduce the hypoglycemia risk with insulin icodec to be comparable to the overall population in the insulin degludec arm
  - Risk of hypoglycemia was always higher in insulin icodec arm within identical %CV subgroups
  - No data were provided to confirm that %CV during the first 2 weeks of treatment is representative of %CV on previous basal insulin therapy
- Pharmacometric modeling assessing changes to basal and bolus components predicted that:
  - Alternative basal titration approaches reduced the risk of hypoglycemia but compromised efficacy
  - 30% reduction in bolus insulin dosing on Days 2-4 maintained glycemic control and optimized safety

*However, no clinical studies were conducted to confirm that patients could successfully titrate bolus insulin differently on specific days of the week without increasing medication errors*

# Backup Slides Shown

# Diabetes Treatment Satisfaction Questionnaire Status (DTSQstatus) Version Treatment Satisfaction Domain

- **Instrument length:** 6 items assess patient satisfaction
- **Recall period:** "Over the past few weeks"
- **Response options:** 7-point rating scale
  - (0) Very unsatisfied
  - (1)
  - (2)
  - (3)
  - (4)
  - (5)
  - (6) Very satisfied
- **Scoring:** Items are summed from the DTSQstatus Treatment Satisfaction domain to generate a total treatment satisfaction score that ranges from 0 to 36, where higher scores indicate greater satisfaction with treatment.
- The DTSQstatus was administered at baseline (Week 0) and Weeks 26 and 52



# Limitations of the DTSQstatus Results

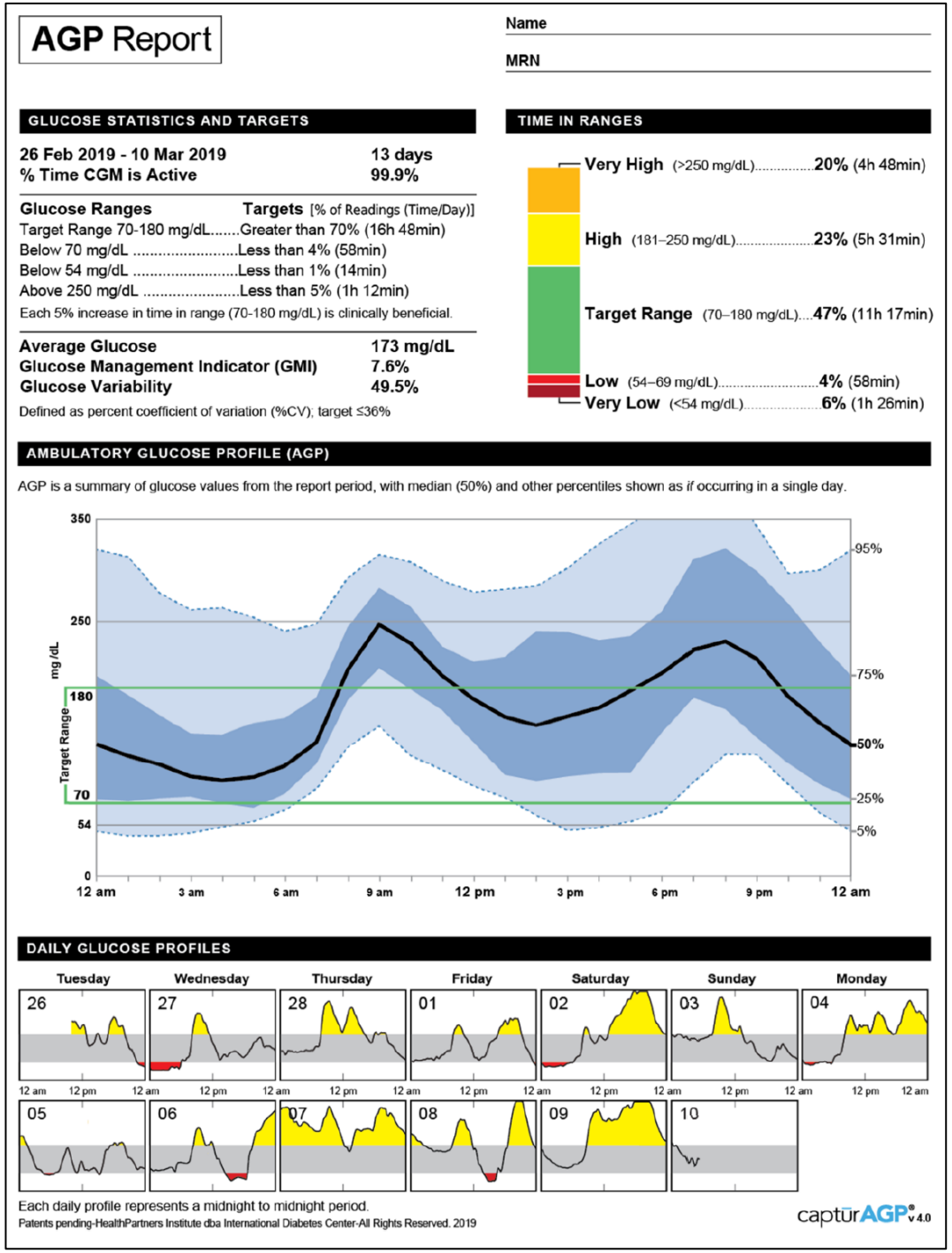
- Change from baseline in DTSQ status Treatment Satisfaction scores after 26 and 52 weeks was nominally different for participants in the insulin degludec group vs. the insulin icodec group in favor of insulin degludec
  - Participants in the insulin degludec arm reported greater treatment satisfaction than participants in the insulin icodec arm

- DTSQstatus results are difficult to interpret due to the following limitations:
  - The DTSQ status Treatment Satisfaction domain assesses satisfaction of patient's current treatment; however, participants were taking more than one current treatment in the trials.
  - It is unknown whether the components of treatment satisfaction in the DTSQs are adequately assessed based on patient and clinician input.
  - The assessment frequency may not be sufficient and may have missed important information on the benefits of the product throughout the trial (DTSQstatus administered at baseline, Week 26 (primary time point), and Week 52).
  - It is unknown what improvement in the total treatment satisfaction score would be meaningful to patients.
  - Limited details regarding the methods used to translate and culturally adapt the DTSQstatus.

# Glycemic Variability

Included in the standard ambulatory glucose profile (AGP) report

- Healthcare professionals use to evaluate the glycemic control for individuals using CGM




Kim JH. Ann Pediatr Endocrinol Metab. 2020;25(3):145-51.

## Serious Adverse Events of Hypoglycemia in ONWARDS 6 (on-treatment)

Insulin icodec:

- 9 subjects (mostly males) experienced 14 SAEs
  (4.66 events/100 PY)
  - n=5 dose reduced
  - n=4 IV glucose administered
  - n=2 glucagon administered

vs

Insulin degludec (data not shown):

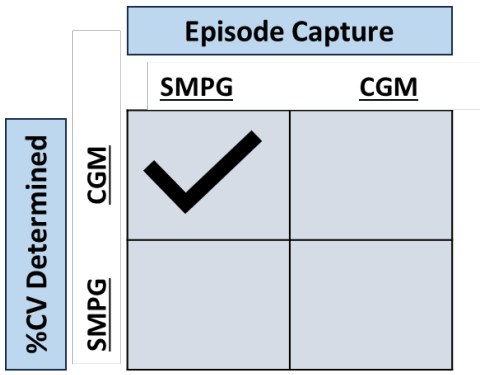
- 3 subjects who experience 3 SAEs
  (1 event/100 PY)
  - n=1 dose not changed
  - n=1 dose reduced
  - n=drug interrupted

*Treatment was not permanently discontinued, and no subjects withdrew due to any of the SAEs in either arm*

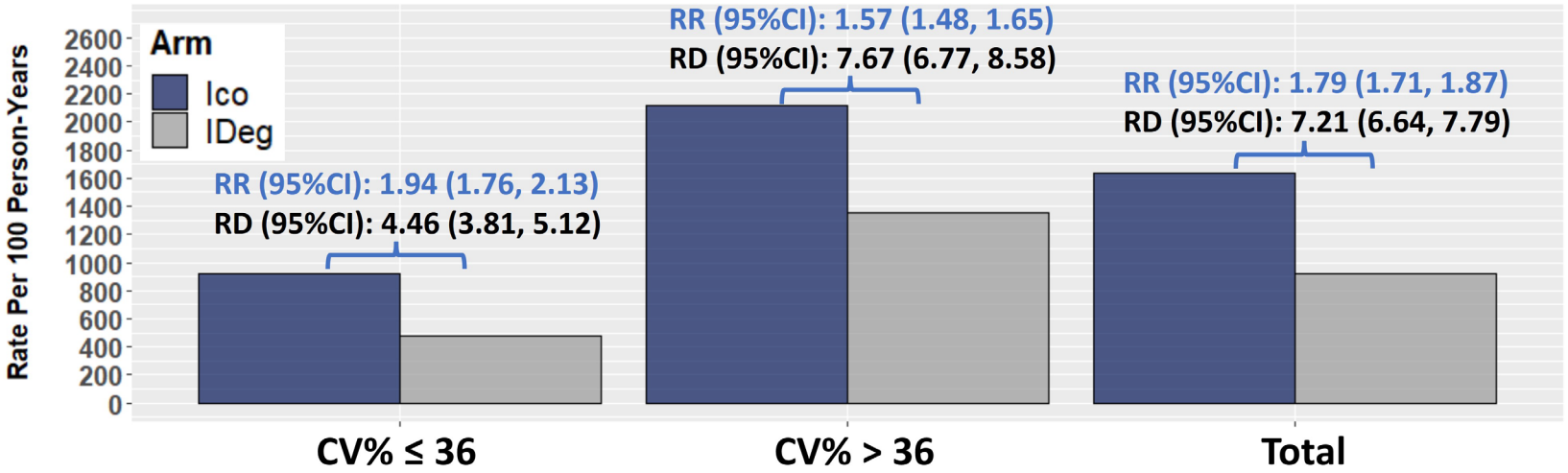
| Ico Subj | Age (y) | Sex | BMI | MedDRA PT | Reported Term | Study Day | Action |
|---|---|---|---|---|---|---|---|
| 1 | 61 | Male | 26.8 | Hypoglycaemia | Severe hypoglycaemia | 17 | Loss of consciousness; IV glucose administered by emergency physician; Dose not changed |
| | | | | Hypoglycaemia | Severe hypoglycaemia | 100 | Loss of consciousness; Dose reduced |
| | | | | Hypoglycaemia | Severe hypoglycaemia | 108 | Loss of consciousness; Carbohydrates administered; Emergency physician contacted; Dose reduced |
| | | | | Hypoglycaemia | Severe hypoglycaemia | 219 | Shaking/sweating/confused; IV glucose administered in ER; Dose not changed |
| 2 | 30 | Male | 36.3 | Hypoglycaemia | Severe hypoglycaemia | 398 | IV glucose administered by paramedics at home |
| 3 | 42 | Male | 27.2 | Hypoglycaemia | Severe hypoglycaemia | 264 | Loss of consciousness; Carbohydrates administered; Dose not changed |
| 4 | 27 | Female | 29.1 | Hypoglycaemia | Severe hypoglycaemia | 129 | Loss of consciousness; Glucagon administered by family member; Medial assistance was requested; Dose reduced |
| 5 | 24 | Male | 16.6 | Hypoglycaemic seizure | Severe hypoglycaemia with seizure | 164 | Loss of consciousness; IV glucose administered in hospital; Dose reduced |
| 6 | 34 | Male | 35.1 | Hypoglycaemia | Severe hypoglycaemia | 99 | Loss of consciousness; IV glucose administered by EMS and hospitalized; Dose reduced |
| 7 | 56 | Male | 26.7 | Hypoglycaemia | Severe hypoglycaemia | 357 | Confusion/dizziness/palpitations, trembling/difficulty speaking; Carbohydrates administered at ER; Dose not changed |
| 8 | 43 | Male | 31.3 | Hypoglycaemia | Severe hypoglycaemia | 225 | Drowsy/sweating/trembling; Carbohydrates administered; Dose reduced |
| | | | | Hypoglycaemia | Severe hypoglycaemia | 253 | Loss of consciousness; Glucagon administered by EMS; Dose not changed |
| | | | | Hypoglycaemia | Severe hypoglycaemia | 363 | Drowsy/sweating/trembling; Carbohydrates administered; Dose reduced |
| 9 | 19 | Male | 25.7 | Hypoglycaemia | Severe hypoglycaemia | 164 | Confusion; Carbohydrates administered; Dose reduced |

Source: Clinical Trial Report, pages 379-387.
Abbreviations: BMI, body mass index; EMS, emergency medical service; EMT, emergency medical technician; ER, emergency room; Ico, insulin icodec; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; y, year

# ONWARDS 6




## Level 2 or 3 Hypoglycemic Episode (SMPG) by %CV (Cutpoint 36%) Weeks 0-57 (Main + Extension)




(CV% Subgroup Determined Using CGM Data)

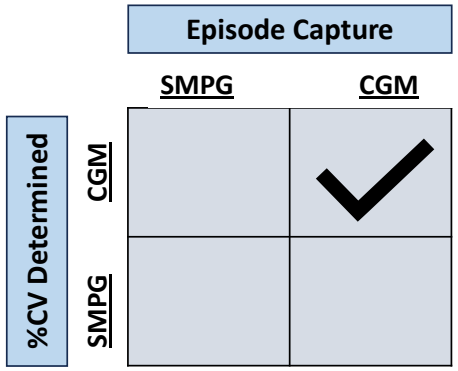
| Level 2 or 3 Hypoglycemic Episode | | | | | | |
|---|---|---|---|---|---|---|
| | %CV ≤ 36 | | %CV > 36 | | Total | |
| | Ico | IDeg | Ico | IDeg | Ico | IDeg |
| N | 112 | 140 | 166 | 140 | 290 | 292 |
| Missing | | | | | 12 | 12 |
| n | 90 | 106 | 162 | 134 | 252 | 240 |
| % | 80.4 | 75.7 | 97.6 | 95.7 | 90.6 | 85.7 |
| E | 1076 | 711 | 3662 | 2035 | 4738 | 2746 |
| Rate | 922.2 | 475.9 | 2121.1 | 1353.8 | 1637.6 | 916.2 |

**Source:** Regulatory Response, February 8, 2024, available from: \\CDSESUB1\evsprod\BLA761326\0042

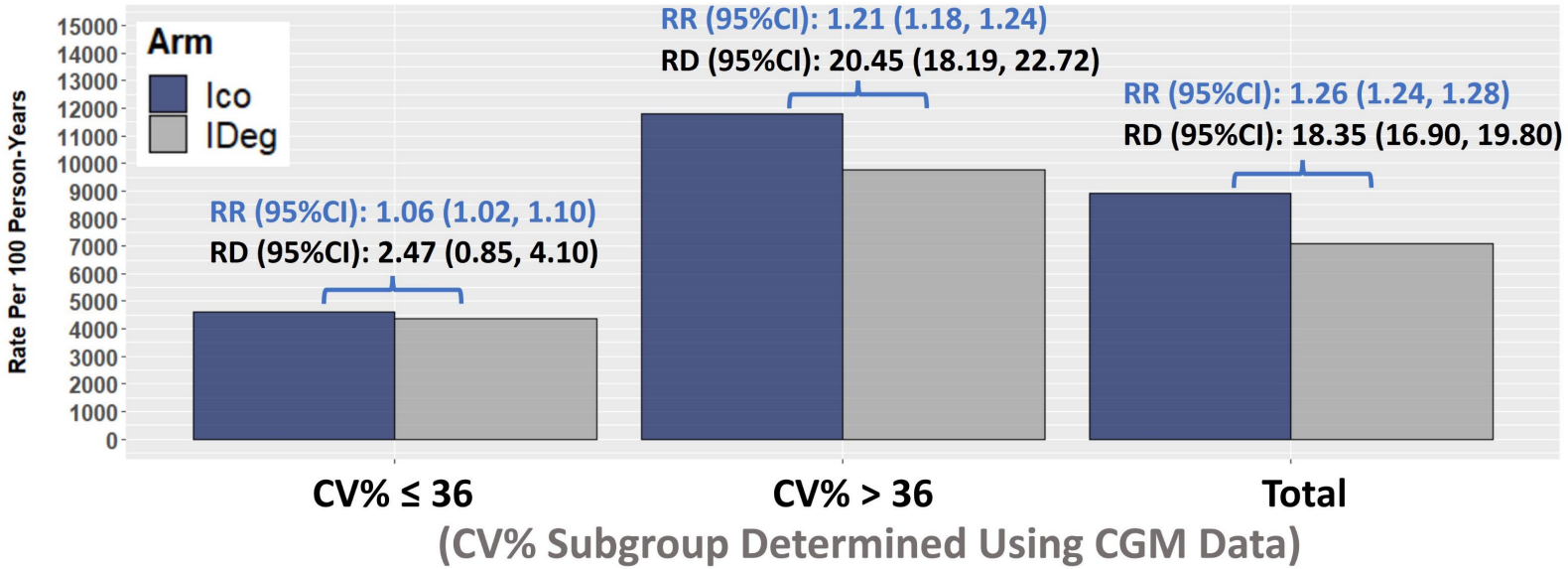
**Note:** RR: crude rate ratio, RD: rate difference. 95% CI were calculated using normal approximation. Considered data for subjects with at least 70% of CGM in Wks 0-2.

**Abbreviations**: n, number of subjects with one or more level 2 or level 3 hypoglycemic episode; %, percentage of subjects with one or more level 2 or level 3 hypoglycemic episode; CV, coefficient of variation; E, number of hypoglycemic episodes; Ins Deg, insulin degludec; Ins Ico, insulin icodec.

# ONWARDS 6




## Level 2 Hypoglycemic Episode (CGM) by %CV (Cutpoint 36%) Weeks 0-57 (Main + Extension)




(CV% Subgroup Determined Using CGM Data)

| Level 2 - Episode Capture: CGM | | | | | | |
|---|---|---|---|---|---|---|
| | %CV ≤ 36 | | %CV > 36 | | Total | |
| | Ico | IDeg | Ico | IDeg | Ico | IDeg |
| N | 112 | 140 | 166 | 140 | 290 | 292 |
| Missing | | | | | 12 | 12 |
| n | 111 | 136 | 166 | 140 | 277 | 276 |
| % | 99.1 | 97.1 | 100.0 | 100.0 | 99.6 | 98.6 |
| E | 5378 | 6517 | 20401 | 14688 | 25779 | 21205 |
| Rate | 4609.0 | 4362.1 | 11816.5 | 9771.0 | 8909.9 | 7074.9 |

**Source:** Regulatory Response, February 8, 2024, available from: \\CDSESUB1\evsprod\BLA761326\0042

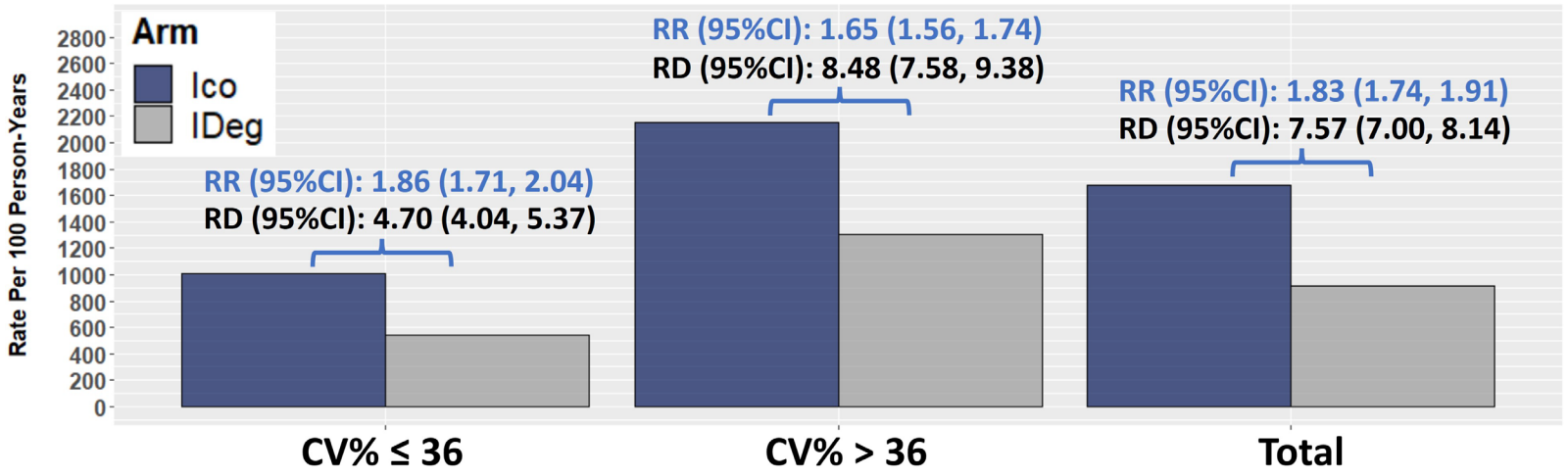
**Note:** RR: crude rate ratio, RD: rate difference. 95% CI were calculated using normal approximation. Considered data for subjects with at least 70% of CGM in Wks 0-2.

**Abbreviations**: n, number of subjects with one or more level 2 or level 3 hypoglycemic episode; %, percentage of subjects with one or more level 2 or level 3 hypoglycemic episode; CV, coefficient of variation; E, number of hypoglycemic episodes; Ins Deg, insulin degludec; Ins Ico, insulin icodec.

# ONWARDS 6

| %CV Determined | Episode Capture: SMPG | Episode Capture: CGM |
|---|---|---|
| CGM | | |
| SMPG | ✓ | |

## Level 2 or 3 Hypoglycemic Episode (SMPG) by %CV (Cutpoint 36%) Weeks 0-57 (Main + Extension)




(CV% Subgroup Determined Using 4-Point SMPG Data)

| Level 2 or 3 - Episode Capture: SMPG | | | | | | |
|---|---|---|---|---|---|---|
| | %CV ≤ 36 | | %CV > 36 | | Total | |
| | Ico | IDeg | Ico | IDeg | Ico | IDeg |
| N | 119 | 168 | 146 | 144 | 290 | 292 |
| Missing | | | | | 3 | 2 |
| n | 98 | 116 | 163 | 133 | 261 | 249 |
| % | 82.4 | 79.5 | 97.0 | 92.4 | 90.9 | 85.9 |
| E | 1267 | 849 | 3719 | 1979 | 4986 | 2828 |
| Rate | 1011.3 | 541.1 | 2154.7 | 1306.5 | 1673.8 | 917.0 |

**Source:** Regulatory Response, February 8, 2024, available from: \\CDSESUB1\evsprod\BLA761326\0042

**Note:** RR: crude rate ratio, RD: rate difference. 95% CI were calculated using normal approximation. Considered data for subjects with at least 70% of CGM in Wks 0-2.

**Abbreviations**: n, number of subjects with one or more level 2 or level 3 hypoglycemic episode; %, percentage of subjects with one or more level 2 or level 3 hypoglycemic episode; CV, coefficient of variation; E, number of hypoglycemic episodes; Ins Deg, insulin degludec; Ins Ico, insulin icodec.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