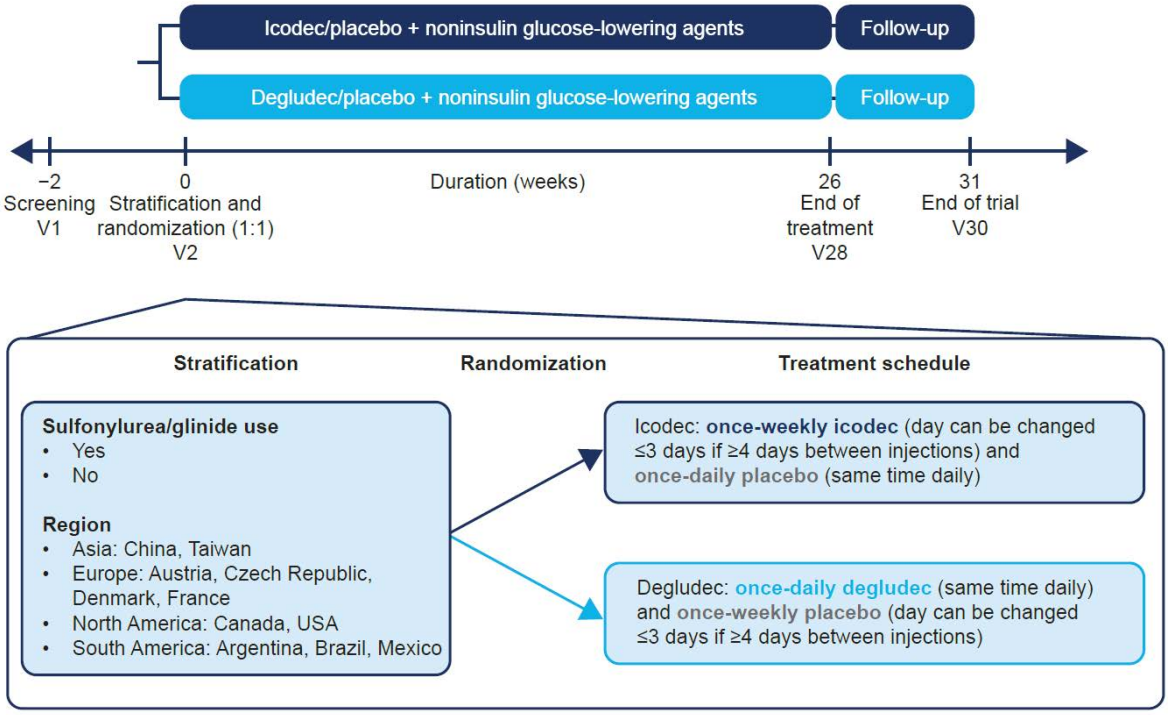
Supplemental Online Content

Lingvay I, Asong M, Desouza C, et al. Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes: The ONWARDS 3 Randomized Clinical Trial. *JAMA.* Published online June 24, 2023. doi:10.1001/jama.2023.11313



This supplemental material has been provided by the authors to give readers additional information about their work.

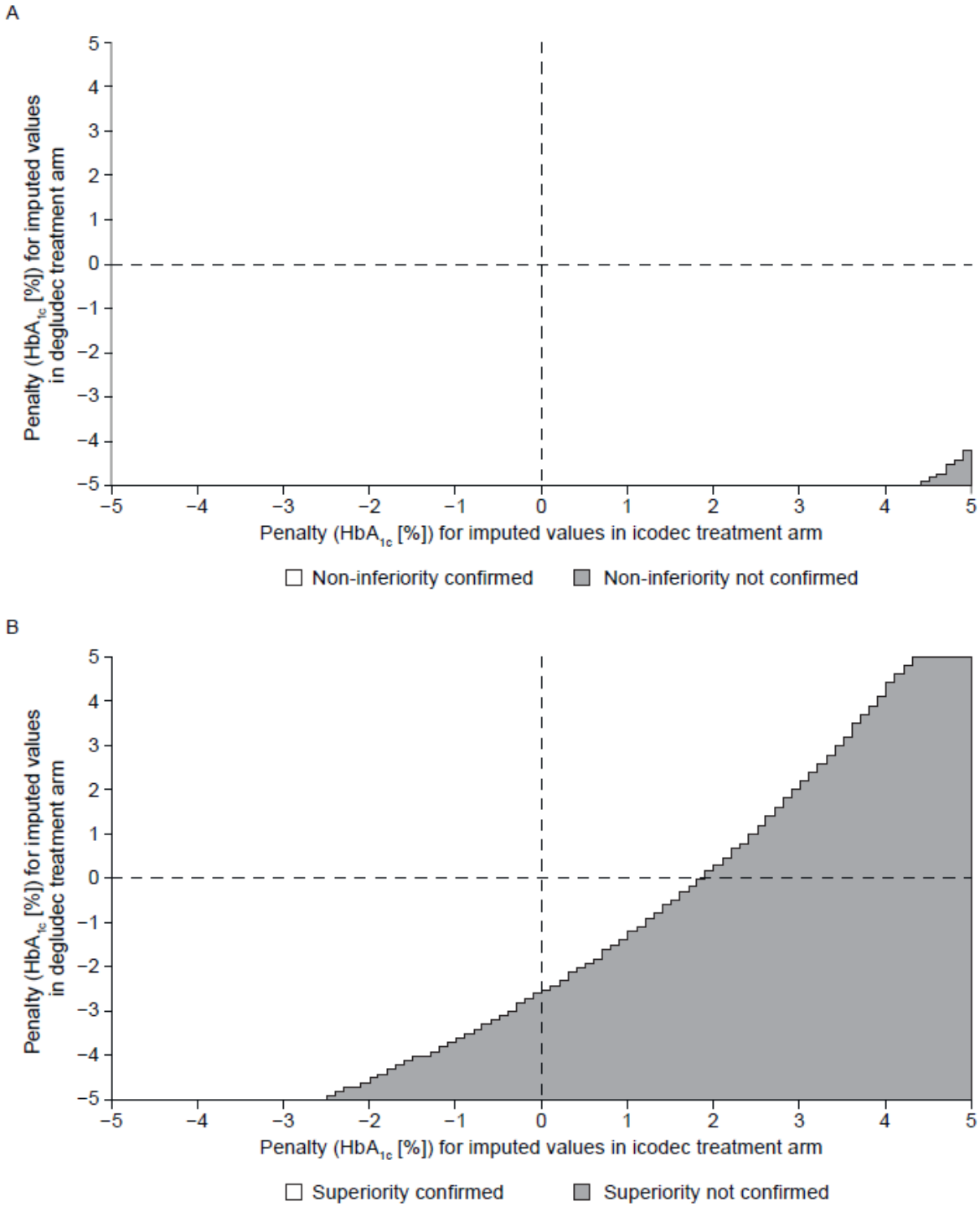
**eFigure 1. Overall Trial Design**




Abbreviations: degludec, insulin degludec; icodec, insulin icodec; V, visit.

Adapted from: Philis-Tsimikas A et al. Diabetes Obes Metab 2023;25:331–41. doi:10.1111/dom.14871. Copyright © 2023. Reproduced with permission of John Wiley & Sons Ltd.

**eFigure 2. Tipping Point Plot for $HbA_{1c}$ Change from Baseline after 26 Weeks**




(A) Plot for noninferiority (FAS). (B) Plot for superiority (FAS).

Abbreviations: degludec, insulin degludec; FAS, full analysis set; $HbA_{1c}$, hemoglobin $A_{1c}$; icodec, insulin icodec.

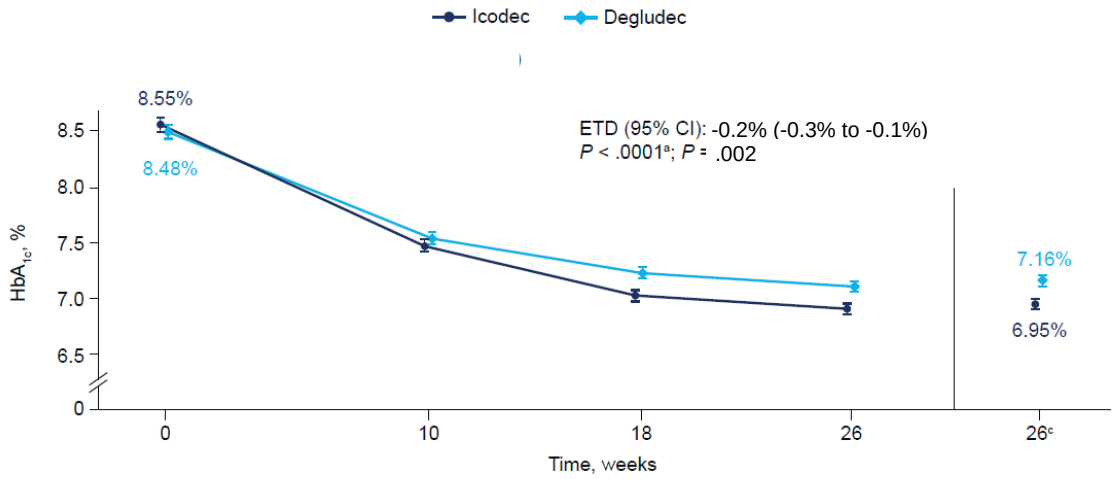
For the primary endpoint, a two-dimensional tipping point analysis was performed where participants with imputed $HbA_{1c}$ measurement at the week 26 visit were assumed to have a worse outcome in the insulin icodec arm and a better outcome in the insulin degludec arm compared with the imputation of the primary analysis.

Panel A, non-inferiority: The conclusion of non-inferiority did not change when the non-inferiority margin of 0.3%-point was added to all icodec participants with an imputed value, or even when all icodec participants with an imputed $HbA_{1c}$ measurement had the value increased by 4%-points, while all participants with an imputed measurement in the degludec arm had the value decreased by 4%-points. This confirms the robustness of the result.

Panel B, superiority: The conclusion of superiority did not change when all icodec participants who had their $HbA_{1c}$ measurement imputed had the value increased by 1.5%-points (while the imputed values for the degludec arm remained unchanged), or when all participants with imputed measurement in the degludec arm had the value decreased by 2%-points (while the imputed values for the icodec arm remained unchanged). This confirms the robustness of the result.

$HbA_{1c}$, hemoglobin A1c. Full analysis set.
Observed data with missing values imputed using multiple imputation.

**eFigure 3. Mean $HbA_{1c}$ Over Time**

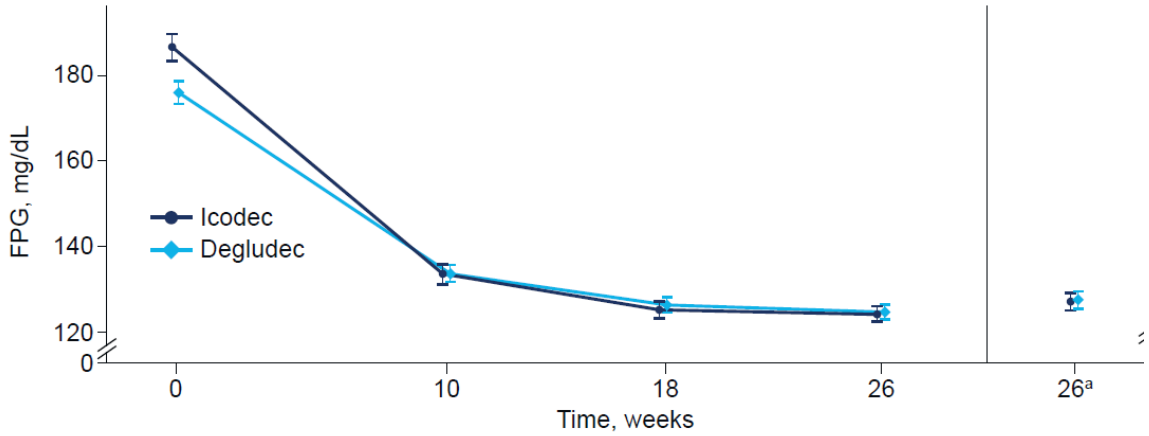



Abbreviations: CI, confidence interval; degludec, insulin degludec; ETD, estimated treatment difference (icodec − degludec); FAS, full analysis set; $HbA_{1c}$, hemoglobin $A_{1c}$; icodec, insulin icodec.

To convert $HbA_{1c}$ to mmol/mol, use the equation $(10.93 \times HbA_{1c}) - 23.50$.

Observed and estimated mean $HbA_{1c}$ (symbols) and SEM (error bars) from baseline over time including data obtained after premature treatment discontinuation (full analysis set). [a]*P* value for noninferiority test of icodec compared with degludec (noninferiority confirmed: 0.3% margin). [b]*P* value for superiority test of icodec compared with degludec (superiority confirmed). [c]Estimated mean at week 26 based on multiple imputation.

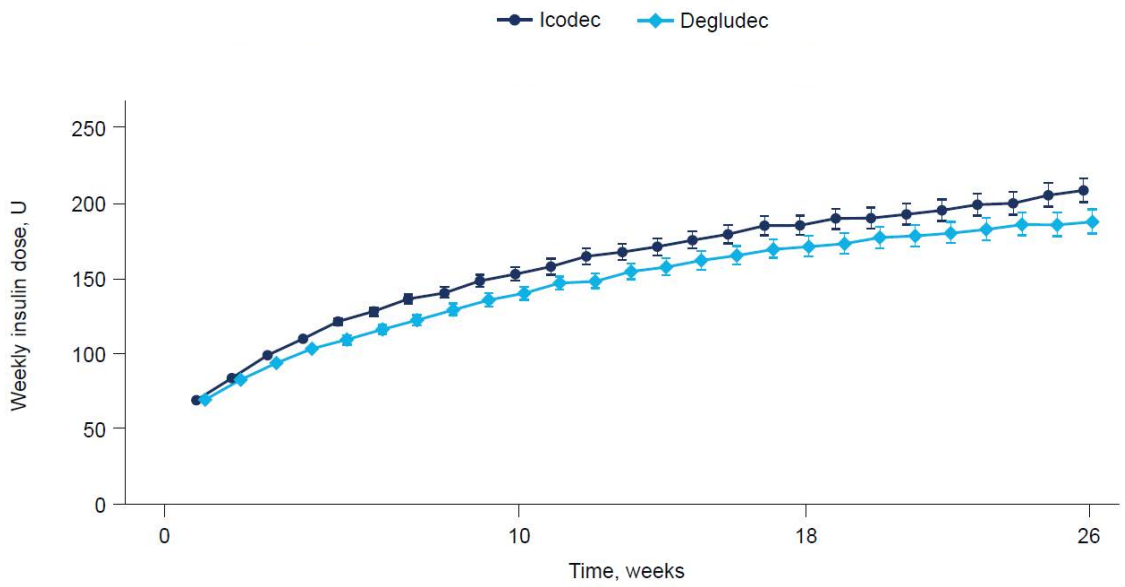
**eFigure 4. Change in Fasting Plasma Glucose Over Time**




Abbreviations: degludec, insulin degludec; FPG, fasting plasma glucose; icodec, insulin icodec.

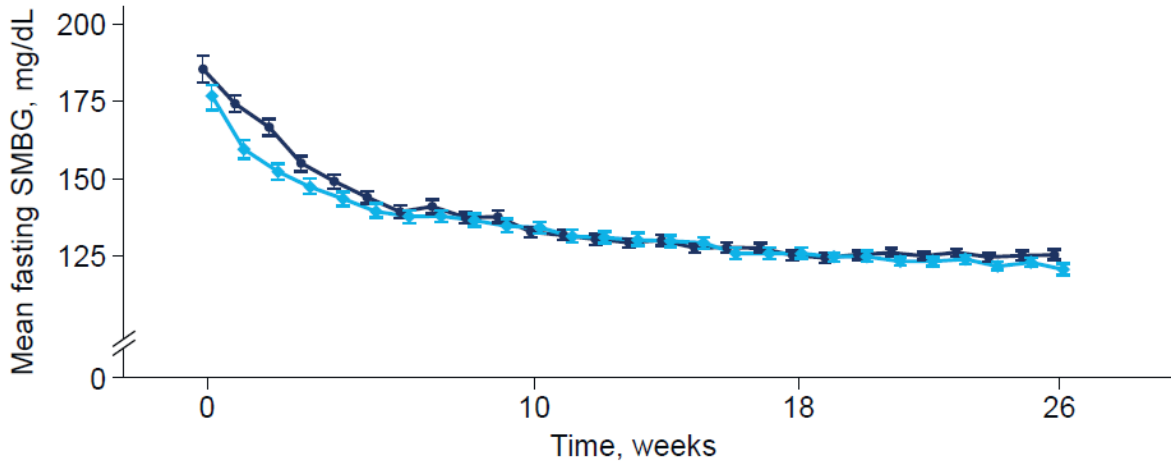
[a]Estimated mean FPG at week 26 derived based on multiple imputation. Observed data are shown as mean (symbols) standard error of the mean (error bars), including data obtained after premature treatment discontinuation (full analysis set).

**eFigure 5. Mean Insulin Dose Over Time**



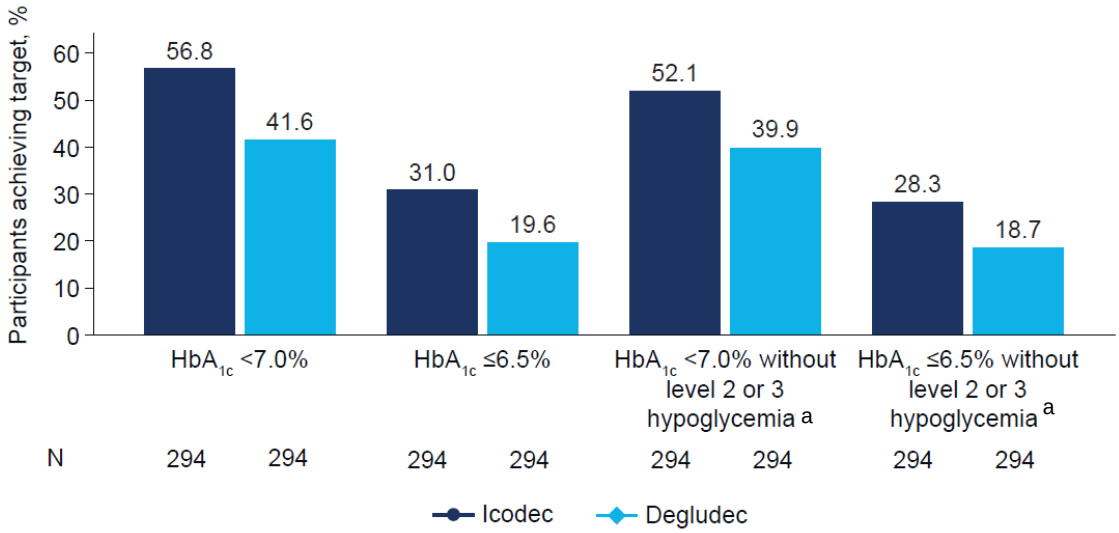

Observed geometric mean total weekly insulin dose (points) and standard error of the mean (error bars) over time (values are back-transformed from log-scale) (safety analysis set).

**eFigure 6. Change in Self-Measured Blood Glucose Over Time**




Abbreviations: degludec, insulin degludec; SMBG, self-measured blood glucose; icodec, insulin icodec.

**eFigure 7. Proportion of Participants Achieving $HbA_{1c}$ Targets With and Without Level 2 or 3 Hypoglycemia**




Abbreviations: degludec, insulin degludec; $HbA_{1c}$, hemoglobin $A_{1c}$; icodec, insulin icodec.

[a]Level 2 or 3 hypoglycemia during the preceding 12 weeks. Level 2 hypoglycemia (clinically significant): plasma glucose value less than 54 mg/dL (<3.0 mmol/L) confirmed by blood glucose meter. Level 3 hypoglycemia (severe): hypoglycemia with severe cognitive impairment requiring external assistance for recovery.

**Table S1. Key Inclusion and Exclusion Criteria**

| **Inclusion criteria** |
|---|
| • Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.<br>• Male or female.<br>• Aged 18 years or older at the time of signing informed consent.<br>• T2D diagnosed ≥180 days prior to the day of screening.<br>• $HbA_{1c}$ of 7.0-11.0% (53-97 mmol/mol), inclusive, at screening, confirmed by central laboratory analysis.<br>• Insulin-naive. However, short-term insulin treatment, lasting for a maximum of 14 days, before the day of screening is allowed, as is prior insulin treatment for gestational diabetes.<br>• Stable daily dose(s) ≥90 days before the day of screening of any of the following noninsulin glucose-lowering agent(s) or combination regimen(s).<br>- Any metformin formulations ≥1500 mg or maximum tolerated or effective dose.<br>- Any metformin combination formulations ≥1500 mg or maximum tolerated or effective dose.<br>- Any of the following oral noninsulin glucose-lowering agent classes including combinations (at least half of the maximum approved dose according to local label or maximum tolerated or effective dose).<br>▪ Sulfonylureas<br>▪ Meglitinides (glinides)<br>▪ DPP-4 inhibitors<br>▪ SGLT2 inhibitors<br>▪ Thiazolidinediones<br>▪ Alpha-glucosidase inhibitors<br>▪ Oral combination products (for the allowed individual oral noninsulin glucose-lowering agents)<br>▪ Oral or injectable GLP-1RAs.<br>• Body mass index ≤40.0 $kg/m^2$. |
| **Exclusion criteria** |
| • Known or suspected hypersensitivity to trial products or related products.<br>• Previous participation in this trial. Participation is defined as signed informed consent.<br>• Women who are pregnant, breast-feeding, or intend to become pregnant, or are of childbearing potential and not using an adequate contraceptive method.<br>• Participation in any clinical trial of an approved or nonapproved investigational medicinal product in the 90 days before screening.[a]<br>• Any disorder, except for conditions associated with T2D mellitus, which in the investigator's opinion might jeopardize participant's safety or compliance with the protocol.<br>• Any episodes of diabetic ketoacidosis in the 90 days prior to the day of screening.[b]<br>• Myocardial infarction, stroke, hospitalization for unstable angina pectoris, or transient ischemic attack in the 180 days prior to the day of screening.<br>• Chronic heart failure, classified as being in NYHA Class IV, at screening.<br>• Planned coronary, carotid, or peripheral artery revascularization.<br>• Renal impairment with estimated glomerular filtration rate value <30 mL/min/1.73 $m^2$ at screening by central laboratory analysis.<br>• Impaired liver function, defined as ALT ≥2.5 times or bilirubin >1.5 times upper normal limit at screening by central laboratory analysis.<br>• Inadequately treated blood pressure, defined as systolic ≥180 mm Hg or diastolic ≥110 mm Hg, at screening.<br>• Treatment with any medication for the indication of diabetes or obesity other than those listed in the inclusion criteria in the 90 days prior to the day of screening. Short-term insulin treatment, lasting for a maximum of 14 days, and prior insulin treatment for gestational diabetes were allowed.<br>• Anticipated initiation or change in concomitant medications (for >14 consecutive days) known to affect weight or glucose metabolism (eg, treatment with orlistat, thyroid hormones, or corticosteroids).<br>• Uncontrolled and potentially unstable diabetic retinopathy or maculopathy.<br>• Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, *in situ* carcinomas of the cervix, or *in situ* prostate cancer) in the 5 years before the day of screening. |

- Anticipated change in lifestyle affecting glucose control.

Abbreviations: ALT, alanine aminotransferase; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor antagonist; $HbA_{1c}$, hemoglobin $A_{1c}$; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

[a]Simultaneous participation in a trial with the primary objective of evaluating an approved or nonapproved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening.

[b]As declared by the participant or in the medical records.

**Table S2. Basal Insulin Titration Algorithm**

| | Prebreakfast SMBG[a] | | Icodec dose adjustment | Degludec dose adjustment |
|---|---|---|---|---|
| **Value to use** | mg/dL | mmol/L | U/week | U/day |
| Mean of the SMBG values | >130 | >7.2 | +20 | +3 |
| | 80-130 | 4.4-7.2 | 0 | 0 |
| Lowest of the SMBG values | <80 | <4.4 | −20 | −3 |

Abbreviations: degludec, insulin degludec; icodec, insulin icodec; SMBG, self-measured blood glucose.

[a]Weekly dose adjustment based on the 3 prebreakfast SMBG values measured on the 2 days before titration and on the day of the titration. If 1 or more SMBG values were missing, the dose adjustment was performed based on the remaining values.

**Table S3. Definitions of In-trial Period and On-treatment Period**

| | |
|---|---|
| **In-trial period** | The in-trial period starts at randomization and ends at the date of:<br>• the last direct participant-site contact<br>• withdrawal for participants who withdraw their informed consent<br>• the last participant-investigator contact, as defined by the investigator for participants who are lost to follow-up (ie, possibly an unscheduled phone visit)<br>• death for participants who die before any of the above. |
| **On-treatment** | The on-treatment period starts at the date of first dose of trial product, as recorded on the eCRF, and ends at the first date of any of the following:<br>• the end of trial visit (week 31)<br>• the last date on trial product +5 weeks for once-daily insulin and +6 weeks for once-weekly insulin (corresponding to 5 weeks after the end of the dosing interval for both treatment arms)<br>• the end-date for the in-trial observation period. |

Abbreviations: eCRF, electronic case report form.

**Table S4. Multiple Imputation Approaches for Relevant Endpoints**

| Measurement | Multiple imputation approach |
|---|---|
| $HbA_{1c}$ at week 26 | Imputed based on the change from LAOT-WOB value for participants who had an intercurrent event and had a measurement at week 26 |
| FPG | Imputed by adding a random error term to baseline values |
| Weekly insulin dose | Imputed based on participants in the degludec arm who completed randomized insulin treatment without bolus insulin initiation for >2 weeks prior to the week 26 visit |
| Bodyweight at week 26 | Imputed based on the change from LAOT-WOB value for participants who had an intercurrent event and had a measurement at week 26 |
| Hypoglycemic episodes | Imputed assuming that the event rate before week 31 followed the respective treatment arm's rate, while the event rate after week 31 was the rate of the degludec arm |

Abbreviations: degludec, insulin degludec; FPG, fasting plasma glucose; $HbA_{1c}$, hemoglobin $A_{1c}$; LAOT-WOB, last available on-treatment value without initiation of bolus insulin for more than 2 weeks.

**Table S5. Observed $HbA_{1c}$ by treatment week**

| | **Once-weekly insulin icodec (N = 294)** | **Once-daily insulin degludec (N = 294)** |
|---|---|---|
| **Week 0** | | |
| **Mean (SD)** | 8.55 (1.11) | 8.48 (1.01) |
| **Median (min; max)** | 8.40 (6.80; 11.60) | 8.35 (6.70; 11.50) |
| **Week 10** | | |
| **Mean (SD)** | 7.47 (0.91) | 7.54 (0.90) |
| **Median (min; max)** | 7.30 (5.90; 10.60) | 7.40 (5.70; 11.60) |
| **Week 18** | | |
| **Mean (SD)** | 7.02 (0.78) | 7.22 (0.86) |
| **Median (min; max)** | 6.90 (5.50; 10.50) | 7.00 (5.20; 10.20) |
| **Week 26** | | |
| **Mean (SD)** | 6.91 (0.75) | 7.10 (0.77) |
| **Median (min; max)** | 6.80 (5.60; 10.30) | 7.00 (5.20; 10.20) |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$;.min, minimum; max, maximum; SD, standard deviation.

**Table S6. Most Common Adverse Events Occurring in at least 2% of Participants**

| | Once-Weekly Icodec (N=293) | | | | Once-Daily Degludec (N=294) | | | |
|---|---|---|---|---|---|---|---|---|
| Patient-years of exposure | 170.9 | | | | 171.1 | | | |
| | n | % | E | R | n | % | E | R |
| Adverse events | 177 | 60.4 | 119 | 299.01 | 167 | 56.8 | 424 | 247.76 |
| Infections and infestations | 84 | 28.7 | 119 | 69.63 | 71 | 24.1 | 95 | 55.51 |
| COVID-19 | 25 | 8.5 | 25 | 14.63 | 14 | 4.8 | 14 | 8.18 |
| Influenza | 16 | 5.5 | 19. | 11.12 | 9 | 3.1 | 9 | 5.26 |
| Nasopharyngitis | 10 | 3.4 | 12 | 7.02 | 12 | 4.1 | 13 | 7.60 |
| Urinary tract infection | 10 | 3.4 | 12 | 7.02 | 4 | 1.4 | 4 | 2.34 |
| Upper respiratory tract infection | 9 | 3.1 | 9 | 5.27 | 7 | 2.4 | 8 | 4.67 |
| Gastroenteritis | 6 | 2.0 | 6 | 3.51 | 3 | 1.0 | 3 | 1.75 |
| General disorders and administration site conditions | 39 | 13.3 | 84 | 49.15 | 20 | 6.8 | 31 | 18.11 |
| Injection site reaction | 9 | 3.1 | 23 | 13.46 | 2 | 0.7 | 2 | 1.17 |
| Pyrexia | 3 | 1.0 | 3 | 1.76 | 6 | 2.0 | 6 | 3.51 |
| Musculoskeletal and connective tissue disorders | 31 | 10.6 | 39 | 22.82 | 36 | 12.2 | 42 | 24.54 |
| Back pain | 10 | 3.4 | 11 | 6.44 | 7 | 2.4 | 7 | 4.09 |
| Arthralgia | 5 | 1.7 | 7 | 4.10 | 6 | 2.0 | 6 | 3.51 |
| Pain in extremity | 3 | 1.0 | 3 | 1.76 | 9 | 3.1 | 10 | 5.84 |
| Eye disorders | 29 | 9.9 | 33 | 19.31 | 17 | 5.8 | 25 | 14.61 |
| Diabetic retinopathy | 15 | 5.1 | 16 | 9.36 | 6 | 2.0 | 7 | 4.09 |
| Nervous system disorders | 29 | 9.9 | 38 | 22.24 | 23 | 7.8 | 32 | 18.70 |
| Headache | 10 | 3.4 | 12 | 7.02 | 7 | 2.4 | 8 | 4.67 |
| Dizziness | 6 | 2.0 | 7 | 4.10 | 6 | 2.0 | 7 | 4.09 |
| Gastrointestinal disorders | 26 | 8.9 | 37 | 21.66 | 30 | 10.2 | 38 | 22.20 |
| Diarrhea | 7 | 2.4 | 7 | 4.10 | 7 | 2.4 | 7 | 4.09 |
| Vomiting | 6 | 2.0 | 8 | 4.68 | 1 | 0.3 | 1 | 0.58 |
| Dyspepsia | 1 | 0.3 | 1 | 0.59 | 6 | 2.0 | 6 | 3.51 |
| Metabolism and nutrition disorders | 20 | 6.8 | 26 | 15.21 | 22 | 7.5 | 24 | 14.02 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Dyslipidemia | 6 | 2.0 | 6 | 3.51 | 8 | 2.7 | 8 | 4.67 |
| Vascular disorders | 12 | 4.1 | 12 | 7.02 | 11 | 3.7 | 16 | 9.35 |
| Hypertension | 7 | 2.4 | 7 | 4.10 | 5 | 1.7 | 7 | 4.09 |

Abbreviations: n: number of participants with one or more events, %: percentage of participants with one or more events, E: Number of adverse events, R: Rate (number of adverse events per 100 PYE), PYE: person years of exposure (1 PYE = 365.25 days). On-treatment: onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit, the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. MedDRA version 24.1.

**Table S7. Occurrence of Diabetic Retinopathy or Maculopathy**

| | Once-weekly insulin icodec (n = 293) | | Once-daily insulin degludec (n = 294) | |
|---|---|---|---|---|
| | Incidence, no. (%) | Events (rate per PYE) | Incidence, no. (%) | Events (rate per PYE) |
| Diabetic retinopathy | 15 (5.1) | 16 (0.09) | 6 (2.0) | 7 (0.04) |
| Diabetic retinopathy or maculopathy[a,b,c] | 19 (6.5) | 21 (0.12) | 12 (4.1) | 15 (0.09) |

Abbreviations: degludec, insulin degludec; icodec, insulin icodec; PYE, patient-years of exposure (1 PYE = 365.25 days).

Reported safety data were based on observed events in the safety analysis set (all randomized patients receiving ≥1 dose of study treatment).

[a]Of the participants who were reported to have diabetic retinopathy or maculopathy in the trial, 6 (32%) of the 19 participants in the icodec arm and 4 (33%) of the 12 participants in the degludec arm had a medical history of diabetic retinopathy or maculopathy prior to initiation of trial product.

[b]Of the diabetic retinopathy or maculopathy events, 3 out of 21 events in the icodec arm and 2 out of 15 events in the degludec arm were evaluated as probably or possibly related to basal insulin.

[c]Includes the following adverse events captured by a predefined Medical Dictionary for Regulatory Activities (MedDRA) search for diabetic retinopathy or maculopathy, encompassing diabetic retinopathy, hypertensive retinopathy, macular oedema, non-proliferative retinopathy, chorioretinal atrophy, epiretinal membrane, macular hole, retinal aneurysm, retinal degeneration, retinopathy, and vitreous floaters.