# Insuline settimanali: dall'innovazione all'applicazione clinica

## INNOVAZIONE

Riccardo FORNENGO

S.S.D. di Diabetologia e Malattie Metaboliche
A.S.L. TO4

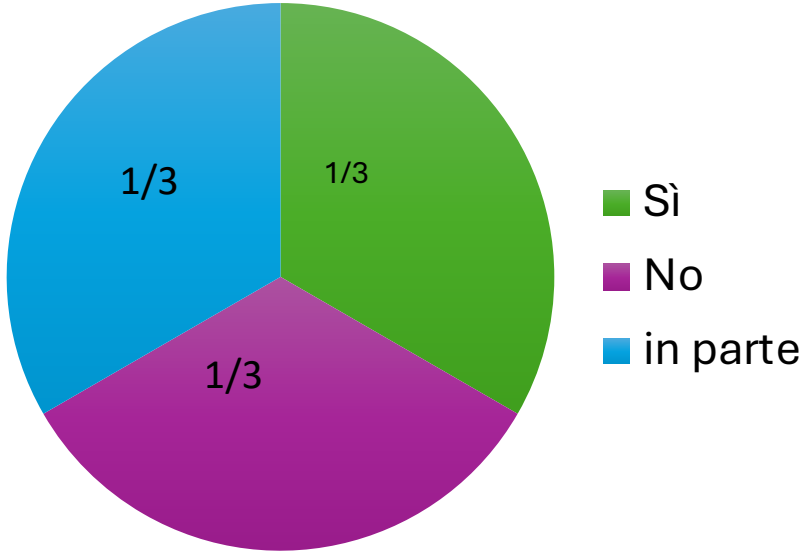
Il dr. RICCARDO FORNENGO dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.

*Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.)*.

# PREMESSE

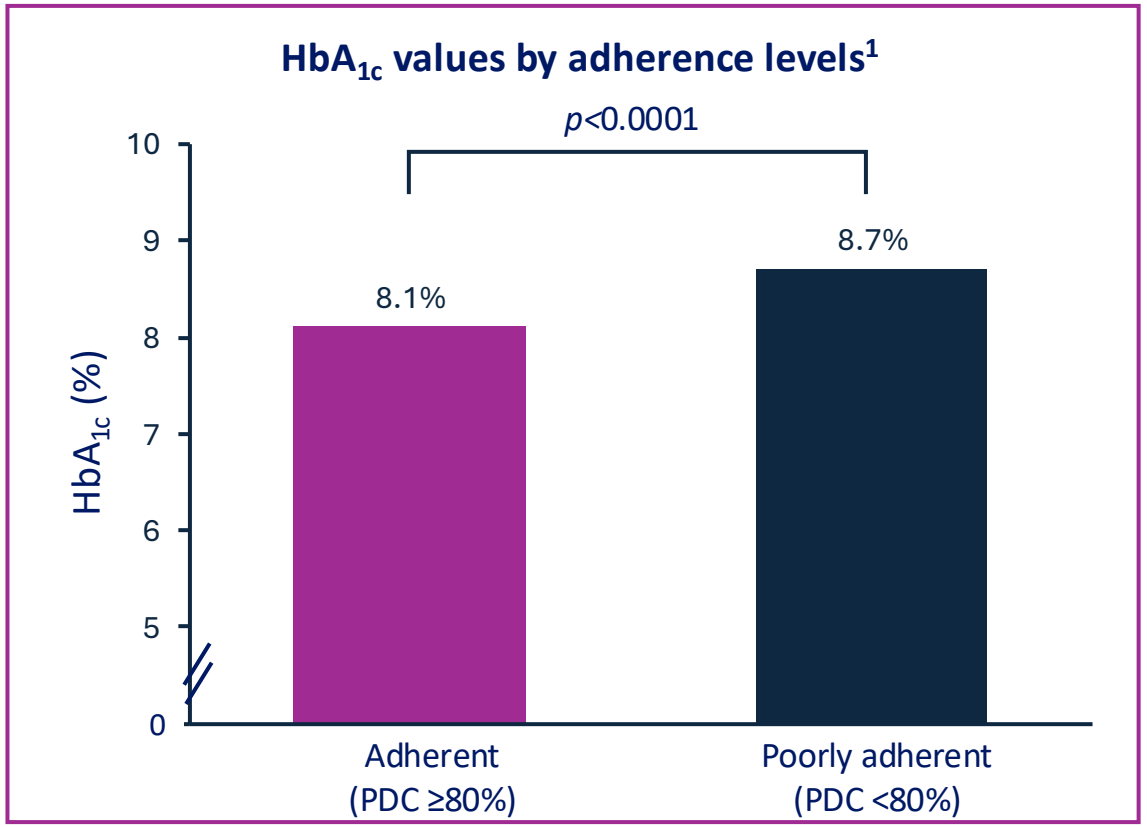
# I pazienti assumono i farmaci?

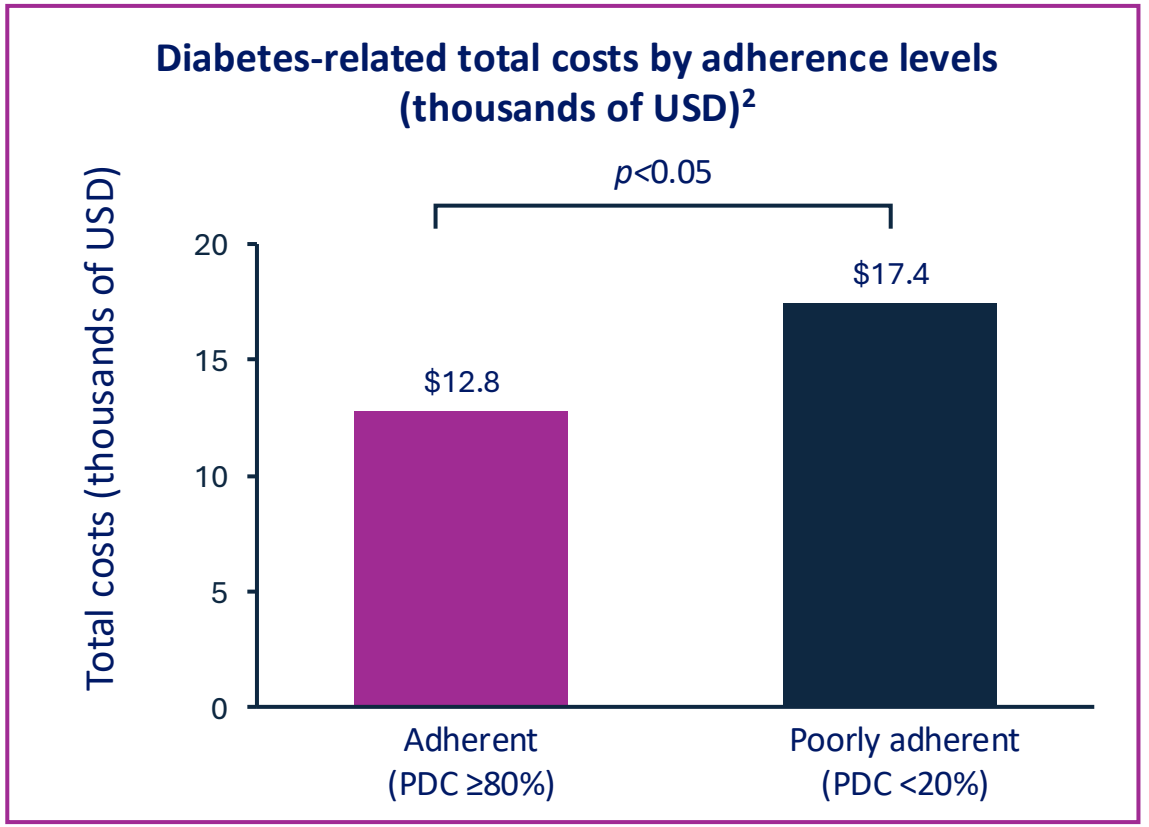
- Solo la metà dei pazienti con patologie croniche assume correttamente i farmaci (dati AIFA).




*[Fialová D et al, Potentially inappropriate medication use among elderly home care patients in Europe.JAMA 2005; 293: 1348-1358].*

# Poor adherence is associated with poor glycaemic control and higher healthcare costs




PDC, proportion of days covered; USD, United States dollar.

1. Donnelly LA et al. *QJM*. 2007;100(6):345–350; 2. Boye KS et al. *Patient Prefer Adherence*. 2016;10:1573–1581.

# Poorly controlled diabetes leads to increased risk of developing diabetes-related complications

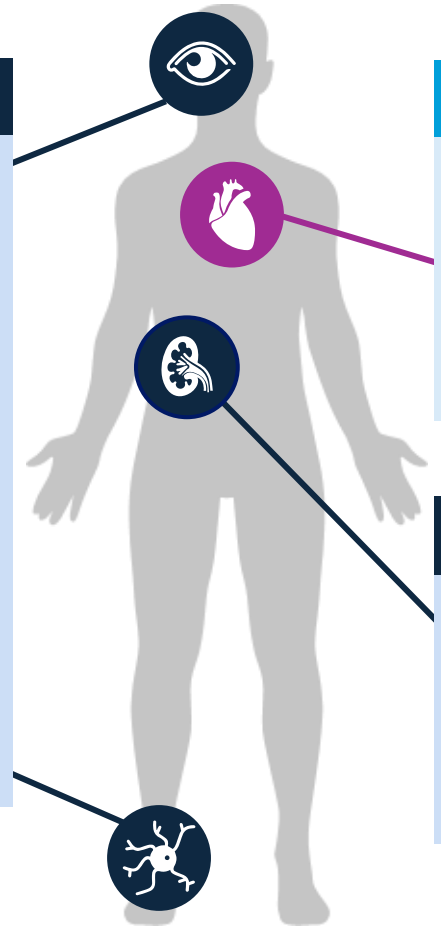
## Microvascular

**Diabetic retinopathy**

- Estimated to affect **35%** of all people with diabetes and is **one of the leading** causes of vision loss in the working age population

**Diabetic neuropathy**

- Nerve damage can lead to ulceration and lower-limb amputations
- **60%** of lower-limb amputations in adults are caused by type 2 diabetes



## Macrovascular

**Cardiovascular disease**

- Includes angina, CAD, MI, stroke, PAD and CHF
- People with diabetes are **two to three times** more likely to have CVD

## Microvascular

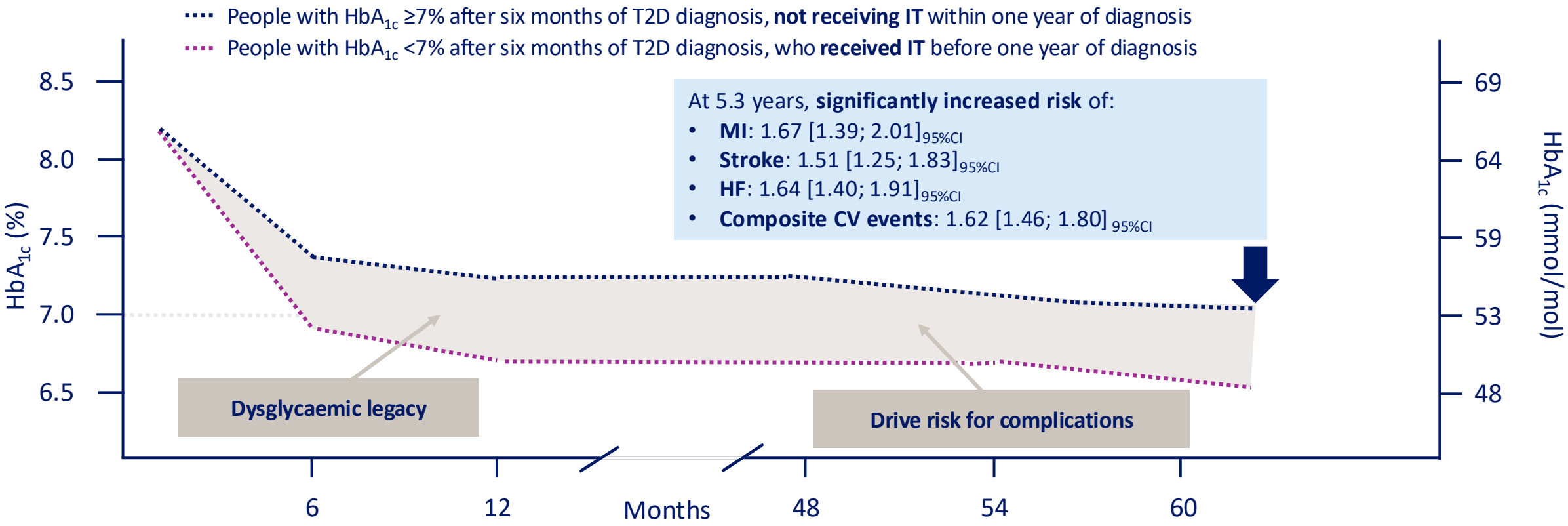
**Diabetic nephropathy**

- Diabetes is a **leading** cause of chronic kidney disease and both conditions are interlinked

CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral artery disease.

1. IDF Diabetes Atlas (9th edition). International Diabetes Federation. 2019. http://www.diabetesatlas.org/. Accessed 23 May 2022.

# Consequences of delayed treatment intensification in people with T2D without previous CVD

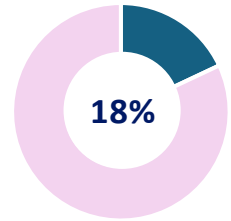



The risk of CVD is shown for people with $HbA_{1c}$ consistently above >7.0% (53 mmol/mol) in the two years following diagnosis for whom treatment intensification is delayed by at least one year versus that of people with $HbA_{1c}$ consistently below <7.0% (53 mmol/mol) in the same period.
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; IT, intensification of treatment; MI, myocardial infarction.

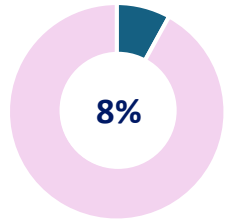
1. Khunti K, Millar-Jones D. *Prim Care Diabetes*. 2017;11(1):3–12; 2. Paul SK et al. *Cardiovasc Diabetol*. 2015;14:100.

# Even one year of poor glycaemic control in people with T2D can result in…

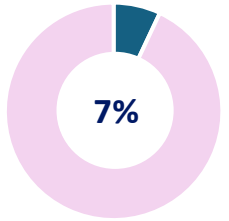
**… an increase** in the cumulative **incidence** of[1]:




Nephropathy

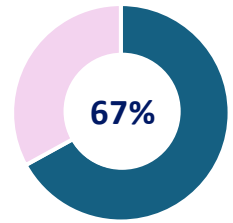



Neuropathy

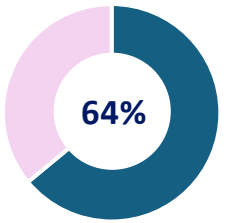



Retinopathy

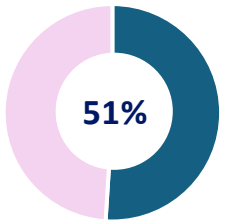
**… a significantly increased risk of[2†]:**



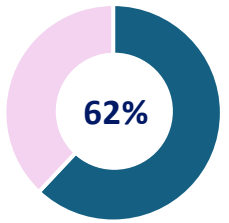

Myocardial infarction




Heart failure



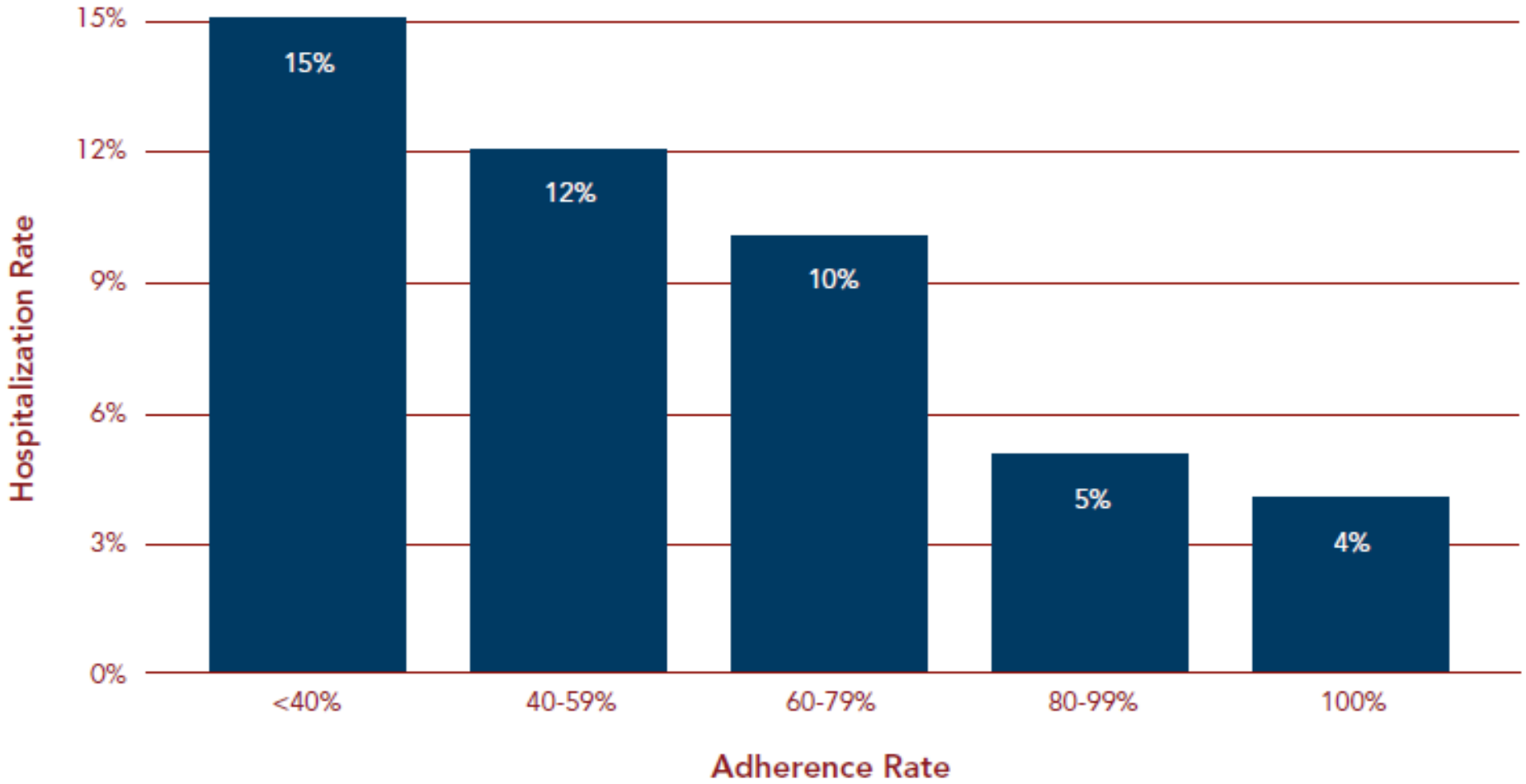

Stroke




Composite CV events‡

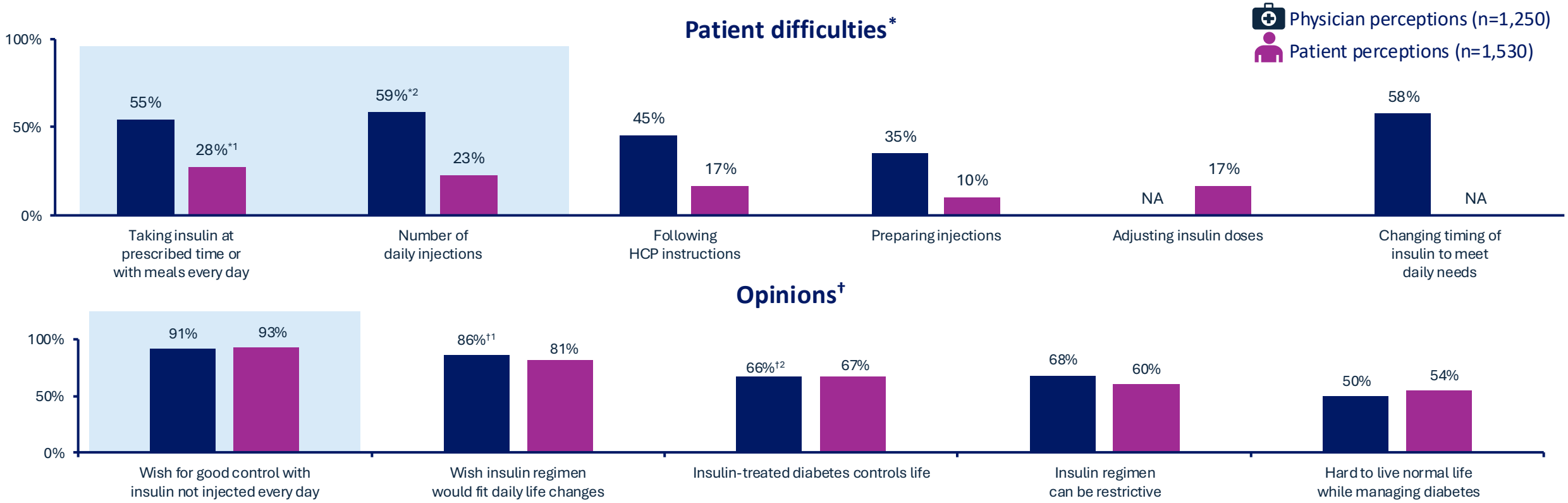
†compared with patients with HbA1c <7%; ‡The composite CV events was based on the occurrence of either myocardial infarction, heart failure or stroke.
**Abbreviations:** CV, cardiovascular; HbA1c, glycated haemoglobin.
**References: 1.** Correa et al. J Gen Intern Med. 2019;34(3):372-378. 2. Paul et al. Cardiovascular Diabetology. 2015;14:100.

## FIGURE 2: RELATIONSHIP BETWEEN ADHERENCE AND HOSPITALIZATION IN PATIENTS WITH DIABETES




Source: D.T. Lau and D. P. Nau, "Oral Antihyperglycemic Medication Nonadherence and Subsequent Hospitalization Among Individuals with Type 2 Diabetes." *Diabetes Care*, September 2004.

# Patients and physicians identify higher frequency of insulin injections as a burden



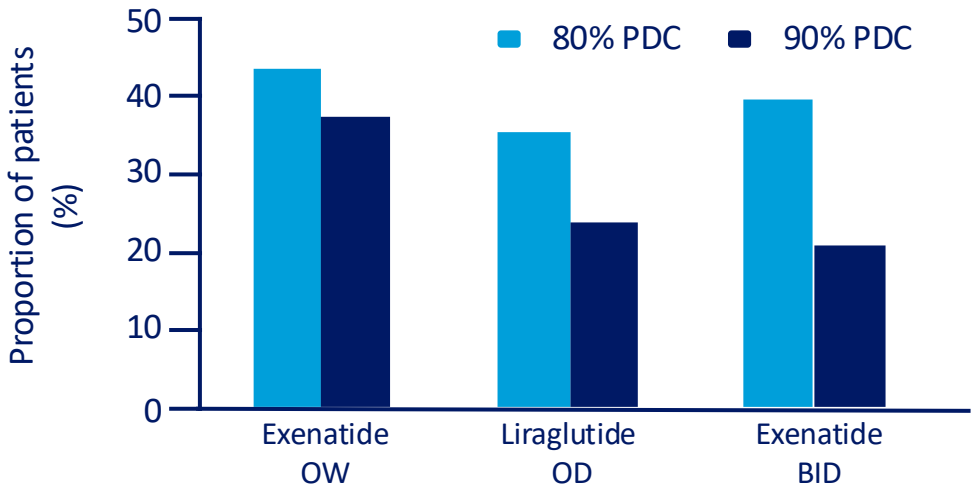

*Very difficult or somewhat difficult (vs. very easy, somewhat easy, not applicable, 'don't know'). Absolute percentages reported for physicians cannot be compared with percentage of patients for whom this is difficult because physicians report whether this is difficult for their 'typical patient' rather than the percentage of their patients for whom this is difficult; rank order of reasons by patients and physicians can be compared. *[1]Average of response for two items (insulin at prescribed times, insulin with each meal). *[2]Physician item is 'taking insulin frequently'. †Strongly agree or somewhat agree (vs. strongly disagree, somewhat disagree, neither, 'don't know'). †Physician item is 'which insulin treatments could be more flexible'. †[2]Physician item is if his/her patients feel diabetes controls their lives. HCP, healthcare professional; n, number of subjects; NA, not asked. 1. Peyrot M et al. *Diabet Med*. 2012;29(5):682–689.

# Example: once-weekly GLP-1RAs have improved treatment satisfaction and adherence

**Improvement in treatment satisfaction with OW exenatide: results from RCTs[1]**

| | Exenatide BID → OW | |
|---|---|---|
| | n* | Change in DTSQ scores |
| Treatment convenience | 123 | 0.42 ± 1.6† |
| Satisfaction continuing treatment | 123 | 0.24 ± 1.3‡ |

**Retrospective cohort study of prescription claims data from US Medicare patients[2]**




**73.1%** of people receiving injectable anti-diabetes medication would be willing to take a once-weekly injectable medication if it was recommended by their physician[3]

*Number of subjects with week 30 and week 52 score. †$p<0.01$. ‡$p\leq0.05$.
BID, twice-daily; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GLP-1RA, glucagon-like peptide-1 receptor agonist; n, number of subjects; OD, once-daily; OW, once-weekly; PDC, proportion of days covered; RCT, randomised controlled trial.
1. Best JH et al. *Diabet Med*. 2009;26(7):722–728; 2. Nguyen H et al. *Adv Ther*. 2017;34(3):658–673; 3. Polonsky WH et al. *Diabetes Obes Metab*. 2011;13(2):144–149.

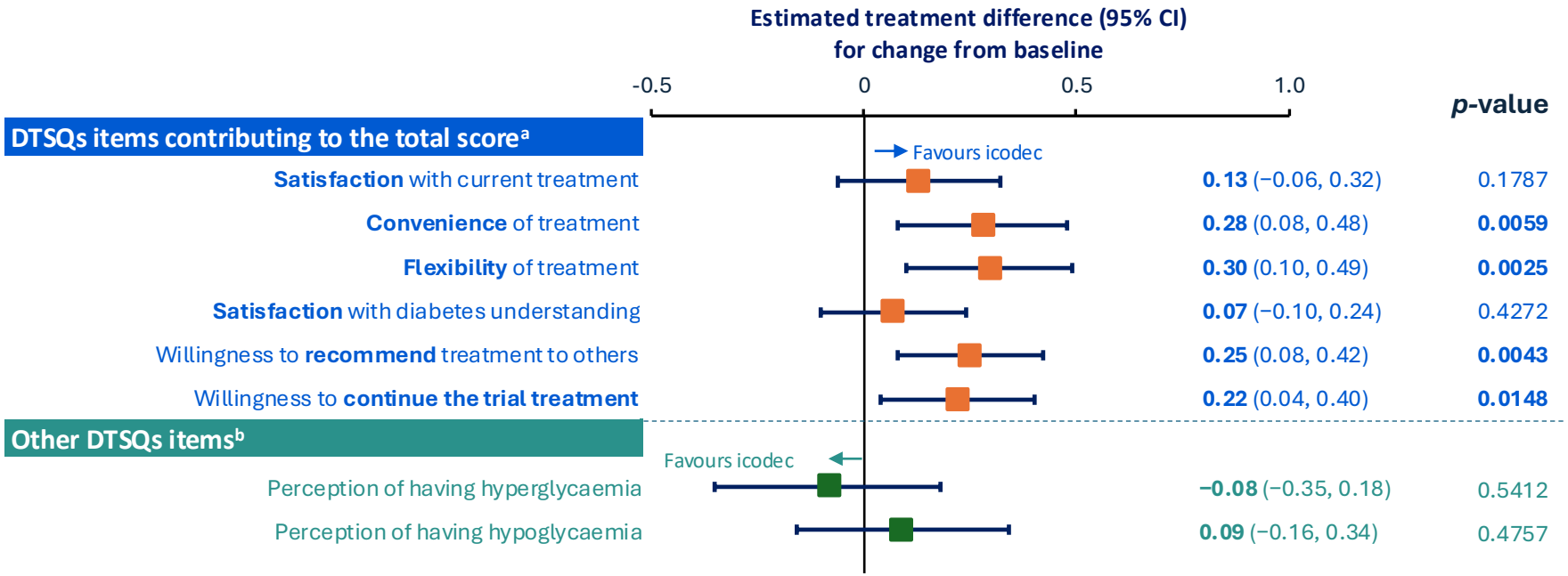
# Diabetes treatment satisfaction questionnaire

| | Question | Option range (scored 0–6) | | |
|---|---|---|---|---|
| 1 | How satisfied are you with your current treatment?* | very dissatisfied | ⟷ | very satisfied |
| 2 | How often have you felt that your blood sugars have been unacceptably high recently? | none of the time | ⟷ | most of the time |
| 3 | How often have you felt that your blood sugars have been unacceptably low recently? | none of the time | ⟷ | most of the time |
| 4 | How convenient have you been finding your treatment to be recently?* | very inconvenient | ⟷ | very convenient |
| 5 | How flexible have you been finding your treatment to be recently?* | very inflexible | ⟷ | very flexible |
| 6 | How satisfied are you with your understanding of your diabetes?* | very dissatisfied | ⟷ | very satisfied |
| 7 | Would you recommend this form of treatment to someone else with your kind of diabetes?* | no, I would definitely not recommend | ⟷ | yes, I would definitely recommend it |
| 8 | How satisfied would you be to continue with your present form of treatment?* | very dissatisfied | ⟷ | very satisfied |

*Six items (1, 4, 5, 6, 7 and 8) contribute to the overall treatment satisfaction score. DTSQ total treatment satisfaction score can range from 0 to 36, with 0 being the lowest and 36 being the highest score.

# Change from baseline in DTSQs scores after 26 weeks

## Icodec basal switch in T2D



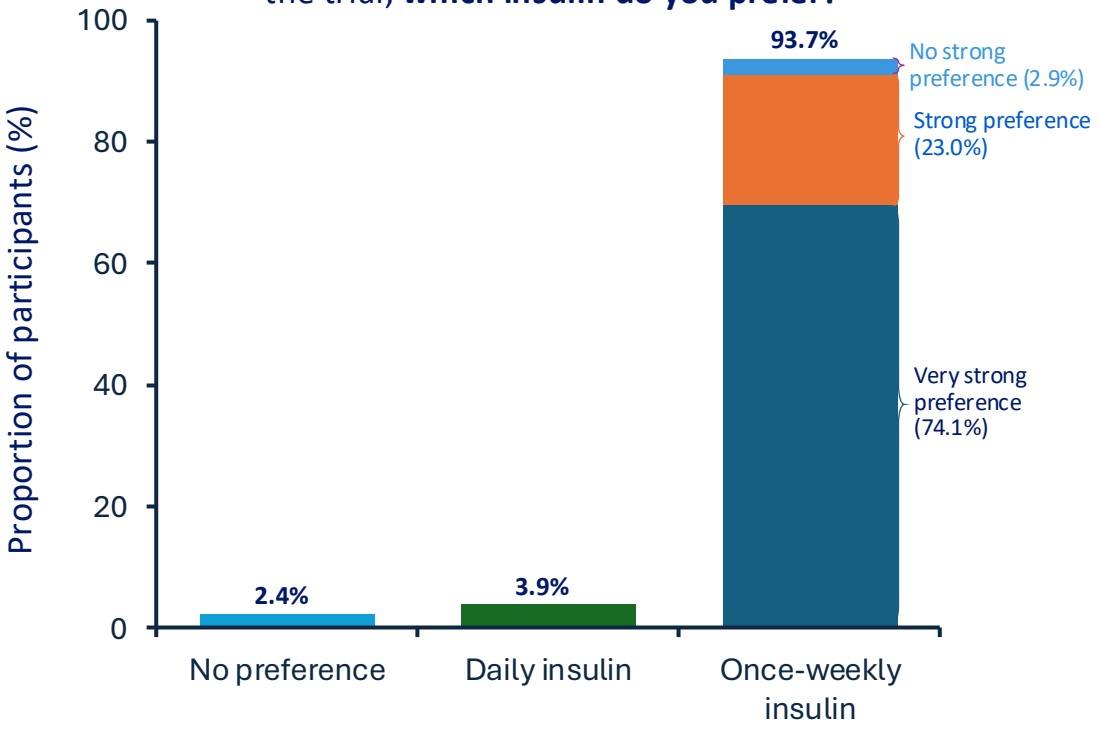

**Statistically significantly greater changes** with icodec versus degludec were seen in **DTSQs total treatment satisfaction score** and DTSQs items on **convenience, flexibility, willingness to continue trial treatment and to recommend treatment to others**

[a]ETD > 0 favours icodec; bETD < 0 favours icodec.
Each item of the DTSQs is scored on a scale from 0 to 6 with higher scores reflecting greater treatment satisfaction. The total treatment score could range from 0 to 36, with 0 being the lowest and 36 being the highest score. In-trial. Full analysis set. No correction for multiplicity. The change from baseline in response after 26 weeks was analysed using an ANCOVA model with treatment, region and personal CGM device use as fixed factors, and baseline response as covariate. Missing values at week 26 were imputed by the baseline value and a random term, using multiple imputation. The random term was normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the LAOT values. The model included the same factors and covariates as the model used for analysis.
p-value: two-sided p-value for test of no treatment difference.
ANCOVA, analysis of covariance; CI, confidence interval; CGM, continuous glucose monitoring; DTSQs, Diabetes Treatment Satisfaction Questionnaire-status; LAOT, last available planned on-treatment.
1. Polonsky W et al. 2023 ESD Annual Meeting. SO-780.

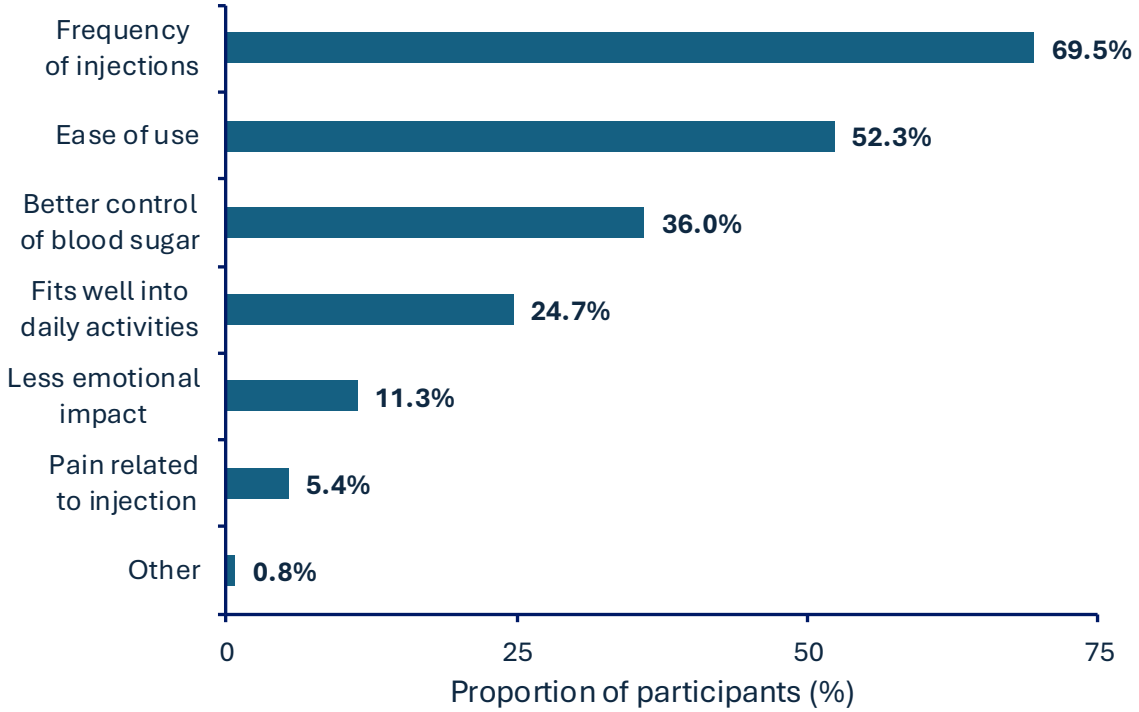
# Insulin Preference Questionnaire (icodec participants)

## Icodec basal switch in T2D

Based on your experience before and during the trial, **which insulin do you prefer?**

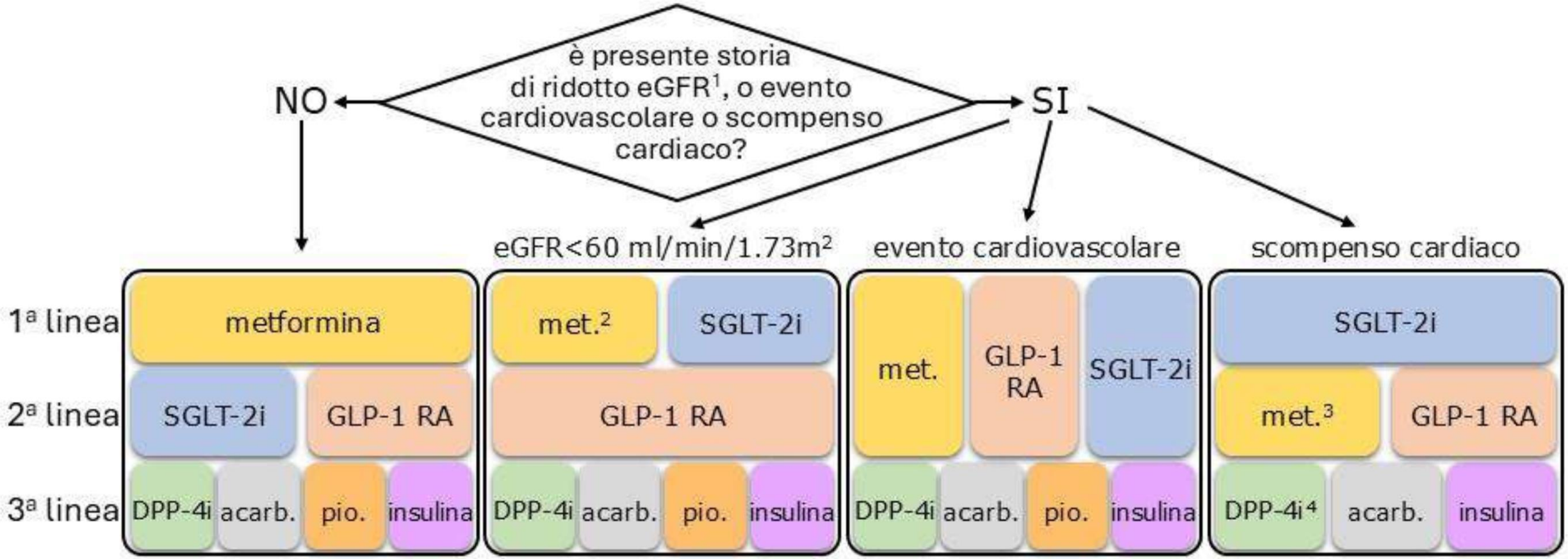



What are the two **main reasons for the preference** for once-weekly insulin?




Majority of the icodec participants had a **very strong preference towards once-weekly insulin icodec** (during the trial) versus their previous daily basal insulin (before the trial)

Pre-trial daily basal insulins were administered once-daily or twice-daily.
Of 263 participants who received insulin icodec, 255 completed the Insulin Preference Questionnaire (239 expressed a preference for once-weekly insulin and provided two reasons each for their preference).
1. Polonsky W et al. 2023 ESD Annual Meeting. SO-780.



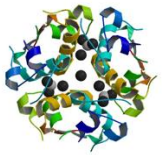
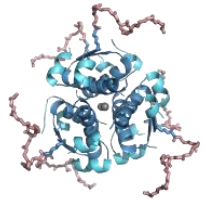

*NB: l'indicazione ai farmaci di terza linea (DPP-4i, acarbosio, pioglitazone, insulina) deve essere considerata solo dopo l'utilizzo in combinazione di metformina, SGLT-2i e GLP-1 RA, qualora tollerati e non controindicati. L'indicazione per DPP-4i è valida solo se GLP-1 RA non indicati o non tollerati. 1. si intende eGFR secondo CKD-EPI < 60 ml/min/1.73m²; 2. se la metformina non è controindicata per eGFR<30 ml/min/1.73m²; 3. se la metformina non è controindicata per ridotta funzione cardiaca; 4. eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.*

*Si raccomanda la deprescrizione di sulfoniluree e repaglinide.*

# Past and present of basal insulin innovation

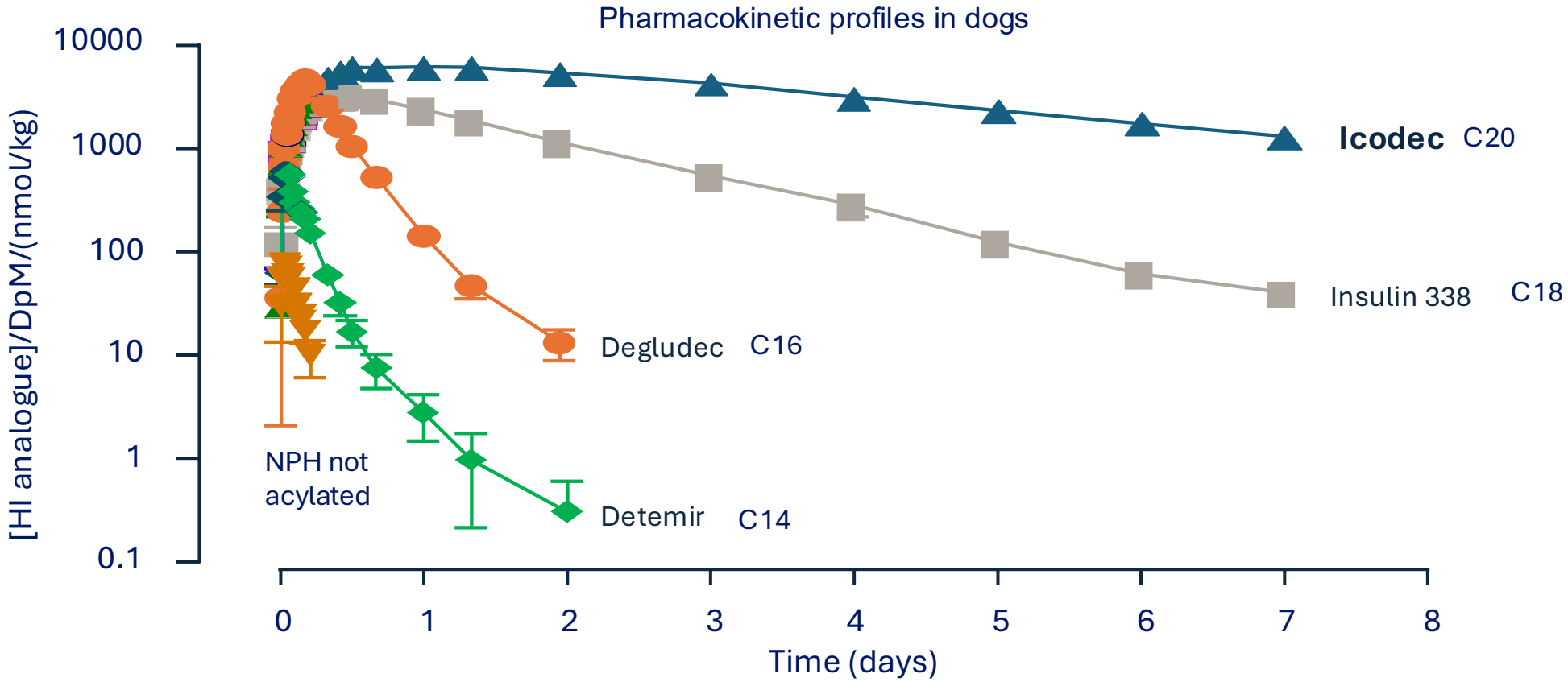
Trying to control absorption of Human Insulin from s.c.

Trying to modify half-life of Human Insulin Analogue

| | Zinc insulin | NPH insulin | 1st generation basal insulin analogues | Ultra long-acting basal insulin analogues | Once-weekly Icodec |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| Half life | **~1 day** | **5–10 hours** | **~0.5 day** | **~1 day** | **~1 week** |
| Admin. | **OD** | **OD/BID** | **OD/BID** | **OD** | **OW** |

BID, twice-daily; NPH, neutral protamine Hagedorn; OD, once-daily; OW, once-weekly.

# Acylated Insulin analogues: fatty acid affinity with albumin increases half-life

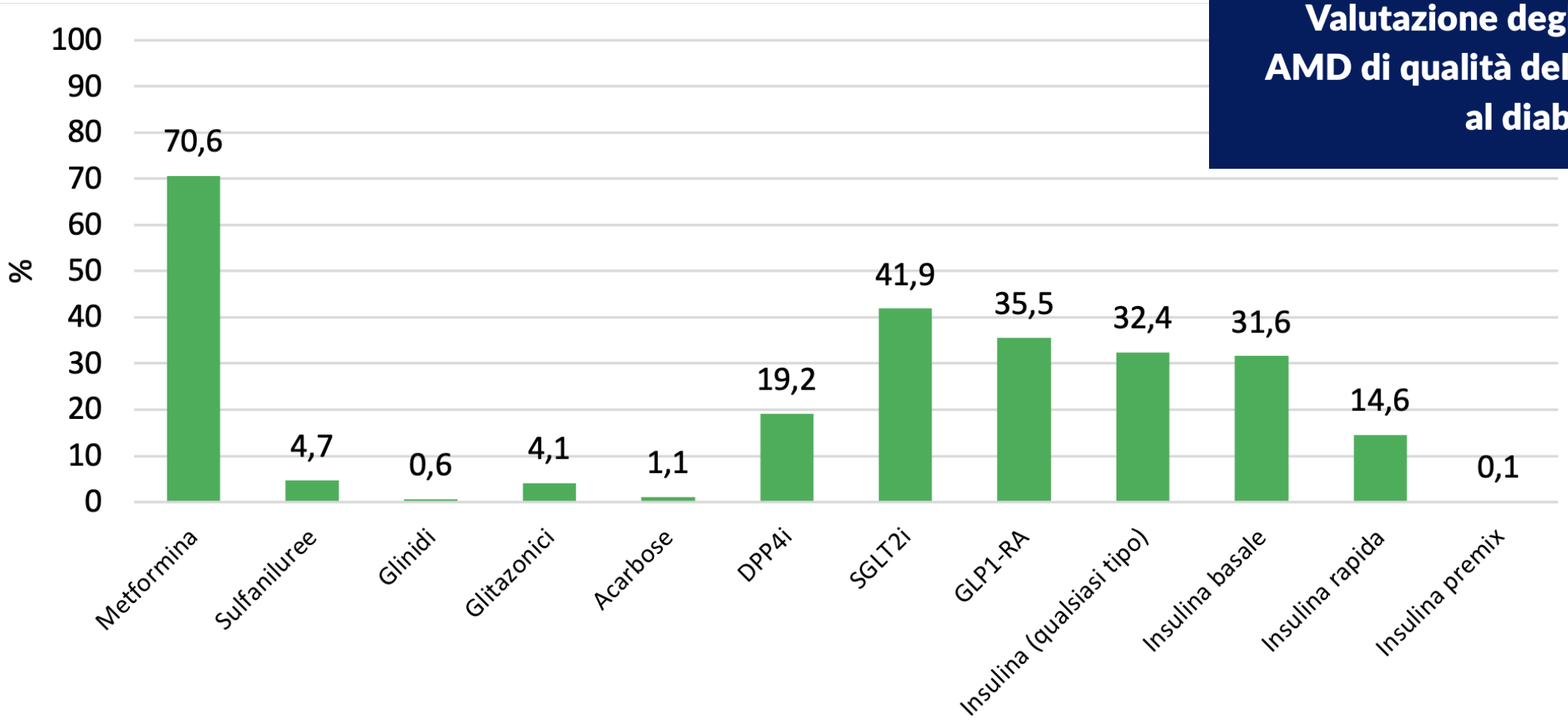



DpM, disintegrations per minute; HI, human insulin; NPH, neutral protamine Hagedorn.

1. Nishimura E et al. *BMJ Open Diab Res Care*. 2021;9(1).

# Uso dei farmaci (%)

## Farmaci per il diabete (%)

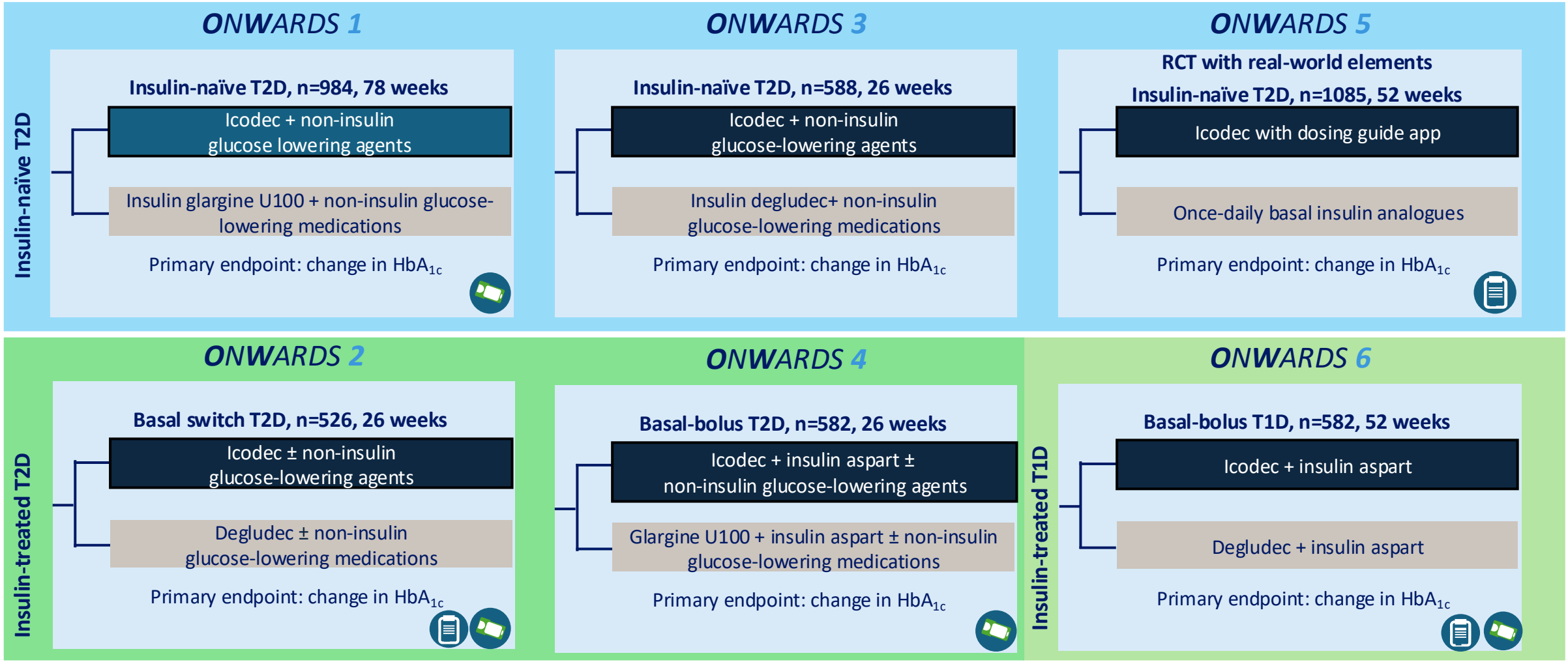




ANNALI AMD 2024

Valutazione degli indicatori AMD di qualità dell'assistenza al diabete in Italia

# Summary of the *ONWARDS* programme




CGM, continuous glucose monitoring; n, number of subjects; PROs, patient reported outcomes; RCT, randomised controlled trial.

1. Philis-Tsimikas A et al. *Diabetes Obes Metab*. 2022;25(2):331-341.

# IPOGLICEMIE

# *CGM metrics in insulin-treated T2D*

## Post-hoc analyses

Objective: To investigate the efficacy and safety of once-weekly icodec versus once-daily degludec or glargine U100 in insulin-treated individuals with T2D using CGM-based metrics and CGM-derived hypoglycaemia duration via ***post-hoc*** **analyses from ONWARDS 2 and 4**

TIR was defined as 3.9–10.0 mmol/L (70–180 mg/dL), TAR as >10.0 mmol/L (>180 mg/dL), and TBR as <3.9 mmol/L (70 mg/dL) and <3.0 mmol/L (54 mg/dL).
CGM; continuous glucose monitoring; TAR, time above range; TBR, time below range; TIR, time-in-range.
1. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10.

# Trial design

## CGM metrics in insulin-treated T2D

### *ONWARDS 2*

**526 individuals**
- T2D treated with OD/BID basal insulin* ± OADs† ± GLP-1RA s.c.
- Age ≥18 years
- $HbA_{1c}$ 7.0–10.0%

**Icodec ± non-insulin glucose-lowering medications**

**Degludec ± non-insulin glucose-lowering medications**


### *ONWARDS 4*

**582 individuals**
- T2D treated with basal insulin* + bolus insulin ± OADs† and GLP-1RA s.c.
- Age ≥18 years
- $HbA_{1c}$: 7.0–10.0%

**Icodec + insulin aspart‡ ± non-insulin glucose-lowering medications**

**Glargine U100 + insulin aspart‡ ± non-insulin glucose-lowering medications**

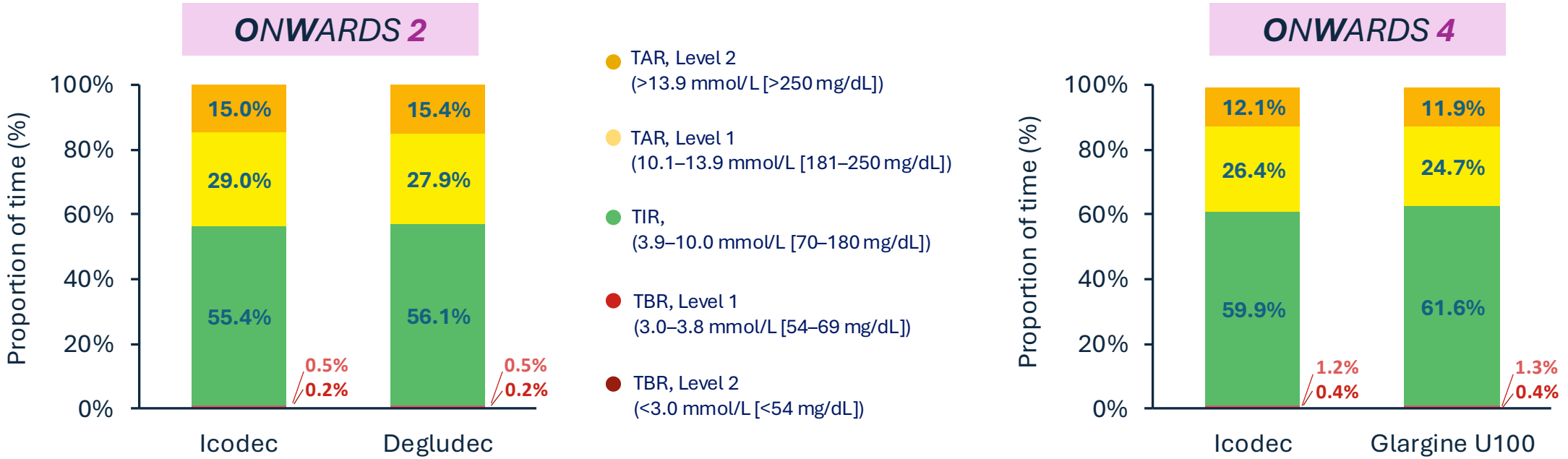

*Participants treated with OD or BID basal insulin (ONWARDS 2) or OD basal insulin (ONWARDS 4). †Sulphonylureas and glinides were discontinued at randomisation to minimise the risk of hypoglycaemia. ‡2–4 daily injections. §Participants were equipped with a CGM device during weeks 0–4 and weeks 22–26

BID, twice daily; CGM, continuous glucose monitoring; GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral glucose-lowering medications; OD, once daily.

1. Philis-Tsimikas A et al. *Diabetes Obes. Metab.* 2022; doi: 10.1111/dom.14871; 2. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10; 3. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425. 4. Mathieu C et al. *Lancet*. 2023;401(10392):1929-40.

# CGM outcomes: Follow-up period (weeks 27–31)

## CGM metrics in insulin-treated T2D







| | TIR 3.9–10 mmol/L (70–180 mg/dL) | TBR <3.9 mmol/L (<70 mg/dL) | TBR <3.0 mmol/L (<54 mg/dL) | TAR >10 mmol/L (>180 mg/dL) |
|---|---|---|---|---|
| ERR or ETD [95% CI] | ETD -1.25 [-4.69;2.18]; *p*=0.474 | ERR 0.91 [0.67;1.24]; *p*=0.548 | ERR 0.85 [0.55;1.31]; *p*=0.466 | 1.27 [-2.22;4.76]; *p*=0.475 |

| | TIR 3.9–10 mmol/L (70–180 mg/dL) | TBR <3.9 mmol/L (<70 mg/dL) | TBR <3.0 mmol/L (<54 mg/dL) | TAR >10 mmol/L (>180 mg/dL) |
|---|---|---|---|---|
| ERR or ETD [95% CI] | ETD -1.45 [-4.88;1.97]; *p*=0.406 | ERR 0.91 [0.71;1.16]; *p*=0.428 | ERR 0.95 [0.69;1.32]; *p*=0.776 | ETD 1.56 [-1.94;5.05]; *p*=0.382 |

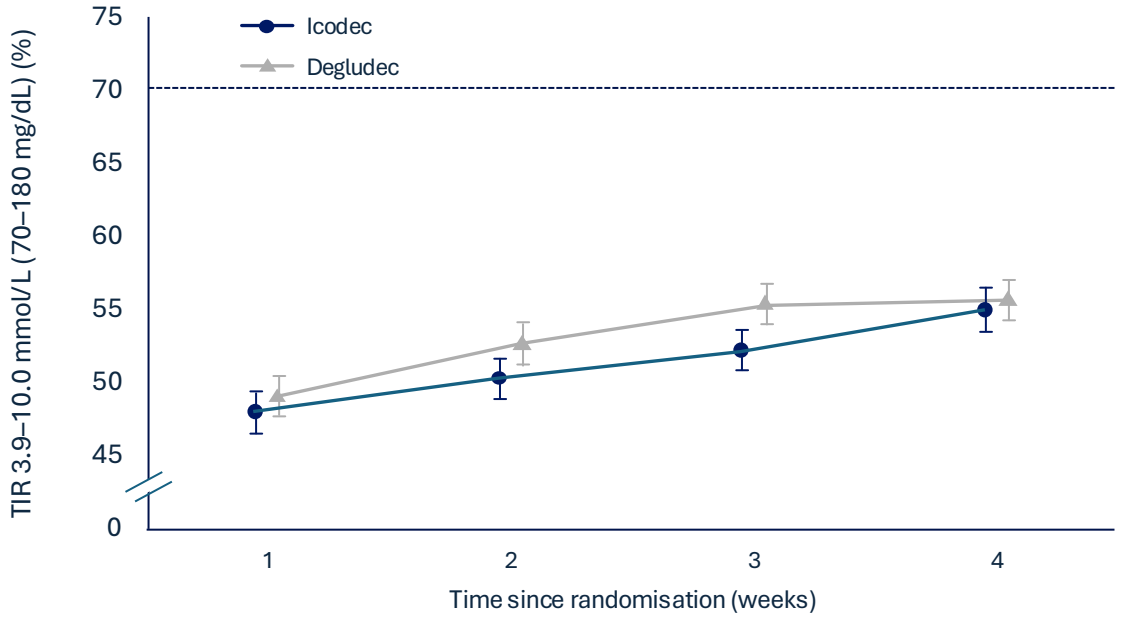
CGM, continuous glucose monitoring; CI, confidence interval; ERR, estimated rate ratio; TIR and TAR analysed with an ANOVA model with region, CGM use, and treatment as fixed factors. TBR analysed with a negative binomial model with a log-link function and the logarithm of the total number of recorded measurements as an offset, with region, treatment, and CGM use as fixed factors. ETD, estimated treatment difference; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.

1. Battelino et al. *Lancet Diabetes Endocrinol.* 2023;11(1):42–57; 2. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10.

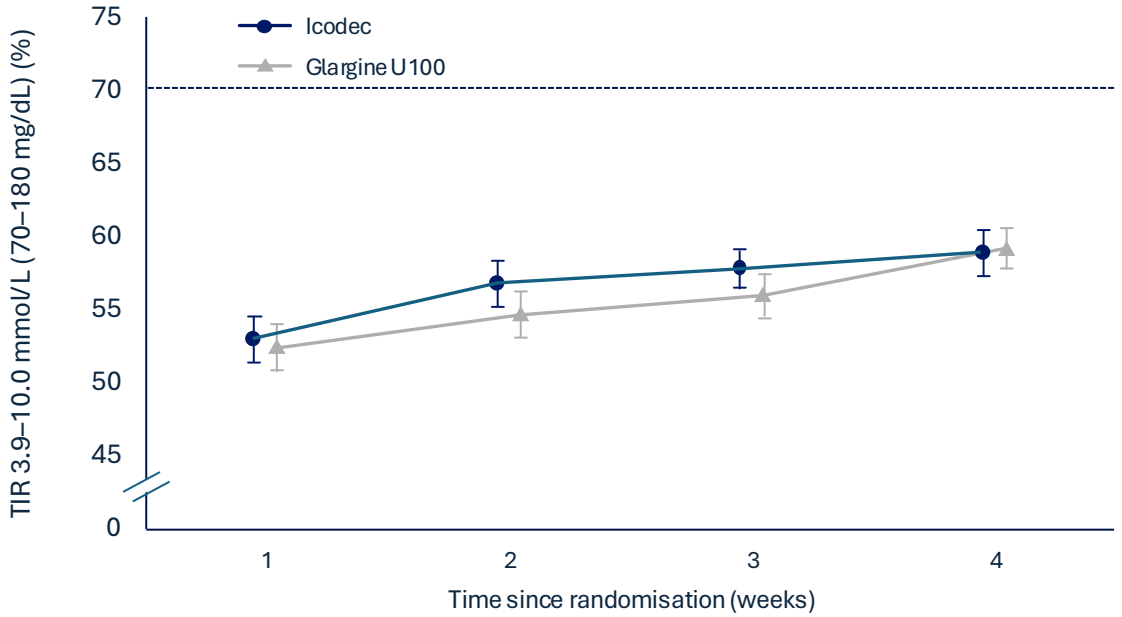
# TIR: Switch period (weeks 0–4)

## CGM metrics in insulin-treated T2D

**ONWARDS 2**




**ONWARDS 4**




Switching to icodec, including a one-time additional 50% icodec dose, **did not compromise glycaemic control (TAR or TIR) versus comparators, and TBR remained within the recommended targets**

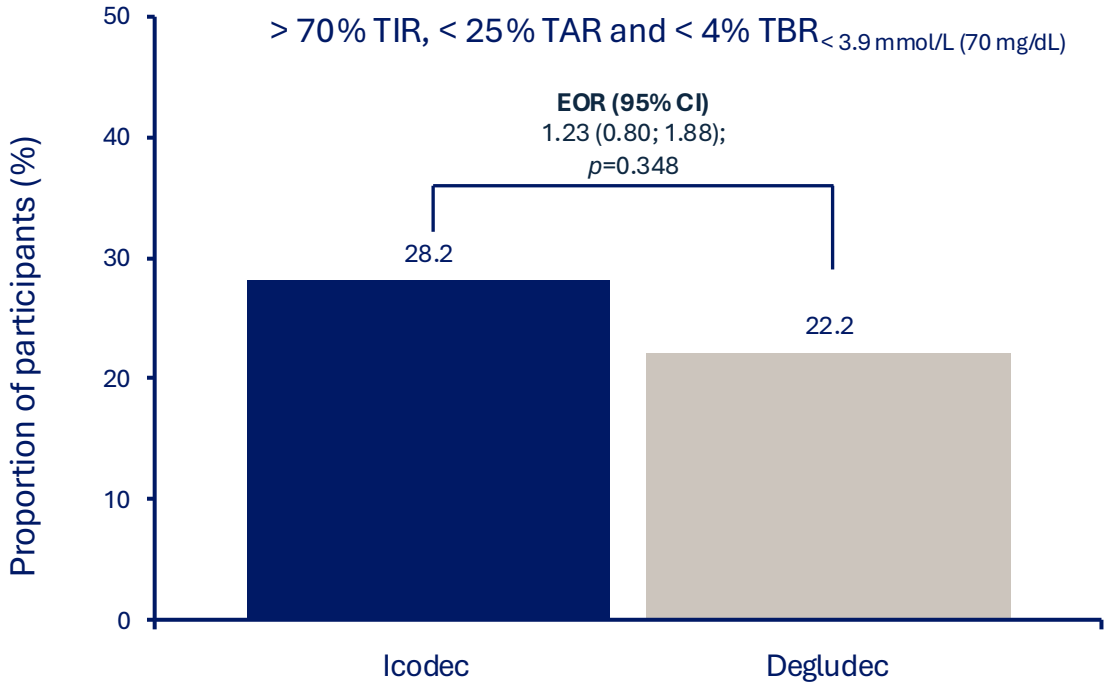
Time spent is defined as 100 times the number of recorded measurements in a given range, divided by the number of recorded measurements. Dashed lines indicate recommended glycaemic targets[1]
TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.

1. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10.

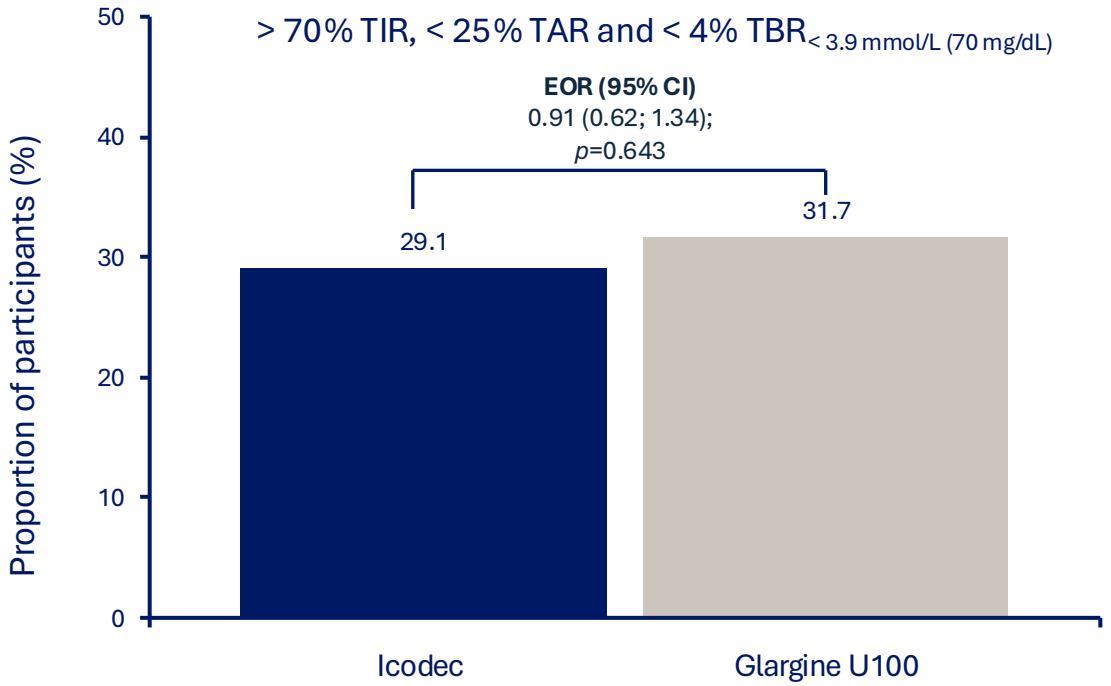
# Proportion of participants achieving CGM targets during steady state period (weeks 22-26)

## CGM metrics in insulin-treated T2D

**ONWARDS 2**




**ONWARDS 4**

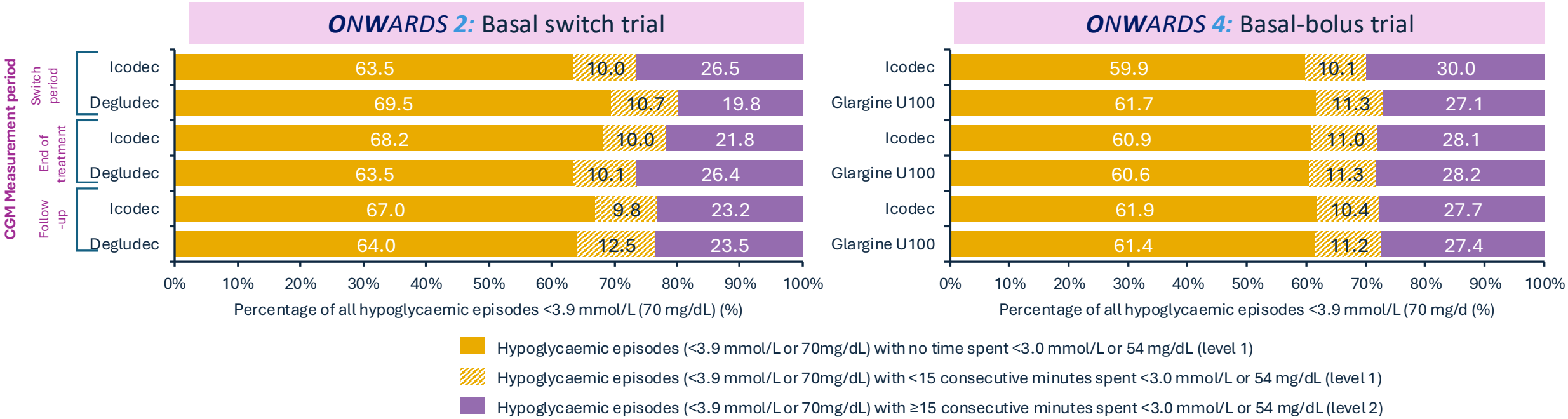



Statistical model: logistic regression. Statistical analysis based on multiple imputed data. Value is the EOR (icodec/degludec [ONWARDS 2]; icodec/glargine U100 [ONWARDS 4]). Statistical model was adjusted for geographic region and use of personal CGM or isCGM device
CGM, continuous glucose monitoring; CI, confidence interval; EOR, estimated odds ratio; isCGM, intermittently scanned CGM; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.

1. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10.

# Classification of CGM-derived overall hypoglycaemic episodes (<3.9 mmol/L) by time spent <3.0 mmol/L

## CGM metrics in insulin-experienced T2D




- During all time periods, most CGM-derived hypoglycaemic episodes <3.9 mmol/L (70 mg/dL) did not include any time spent <3.0 mmol/L (54 mg/dL), or had <15 minutes spent <3.0 mmol/L (54 mg/dL) (level 1)
- There were no substantial differences between icodec and OD comparators in the percentage of CGM-derived hypoglycaemic episodes with time spent <3.0 mmol/L (54 mg/dL) for ≥15 minutes (level 2)

CGM, continuous glucose monitoring; OD, once-daily

1. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10.

# Summary

## CGM metrics in insulin-treated T2D

### In insulin-treated participants with T2D:

During the switch period, TIR, TAR and TBR were not significantly different between OW icodec and OD comparators

The CGM-derived duration of overall hypoglycaemic episodes <3.9 mmol/L (70 mg/dL) was comparable between OW icodec compared with OD comparators during all three CGM time periods, with all medians ≤ 40 minutes

Switching to once-weekly icodec, with a one-time additional 50% icodec dose, showed:
- No increase in TAR versus once-daily basal insulin comparators
- TBR remained within the international recommended CGM targets in all groups

For individuals receiving icodec, the majority of all hypoglycaemic episodes <3.9 mmol/L (70 mg/dL) did not develop into level 2 hypoglycaemia (<3.0 mmol/L [54 mg/dL] for ≥ 15 minutes) during any of the CGM time periods

During the steady state period, TIR and TAR were not significantly different between once-weekly icodec and once-daily comparators:
- TBR remained within the international recommended CGM targets in all groups

CGM, continuous glucose monitoring; OD, once-daily; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.

1. Bajaj H et al. *Diabetes Care*. 2024;47(4):1–10.

# ASSOCIAZIONI CON GLP-1

# *Efficacy and hypoglycaemia outcomes in T2D according to **baseline GLP-1RA use**: ONWARDS 1–5*

Post-hoc analyses

**Aim**: This post-hoc analysis of ONWARDS 1–5 assessed the treatment effects of OW icodec versus OD basal insulin comparators according to baseline GLP-1RA use in individuals with T2D

- Pretrial GLP-1RA use was recommended to be continued in all trials, but participants were not stratified by baseline GLP-1RA use upon randomisation
- Per protocol, participants had to be treated with a stable dose of GLP-1RA for at least 90 days prior to screening

**Treatment outcomes assessed by trial according to GLP-1RA use at baseline**

- Estimated treatment difference in change in $HbA_{1C}$ from baseline to EOT[a]
- Observed rates of clinically significant or severe hypoglycaemia[b]
- Estimated proportion of participants achieving $HbA_{1C}$ <7% at EOT without clinically significant or severe hypoglycaemic episodes in the previous 12 weeks
- Estimated mean weekly basal insulin dose during the last 2 weeks of treatment
- Estimated change in body weight from baseline to EOT

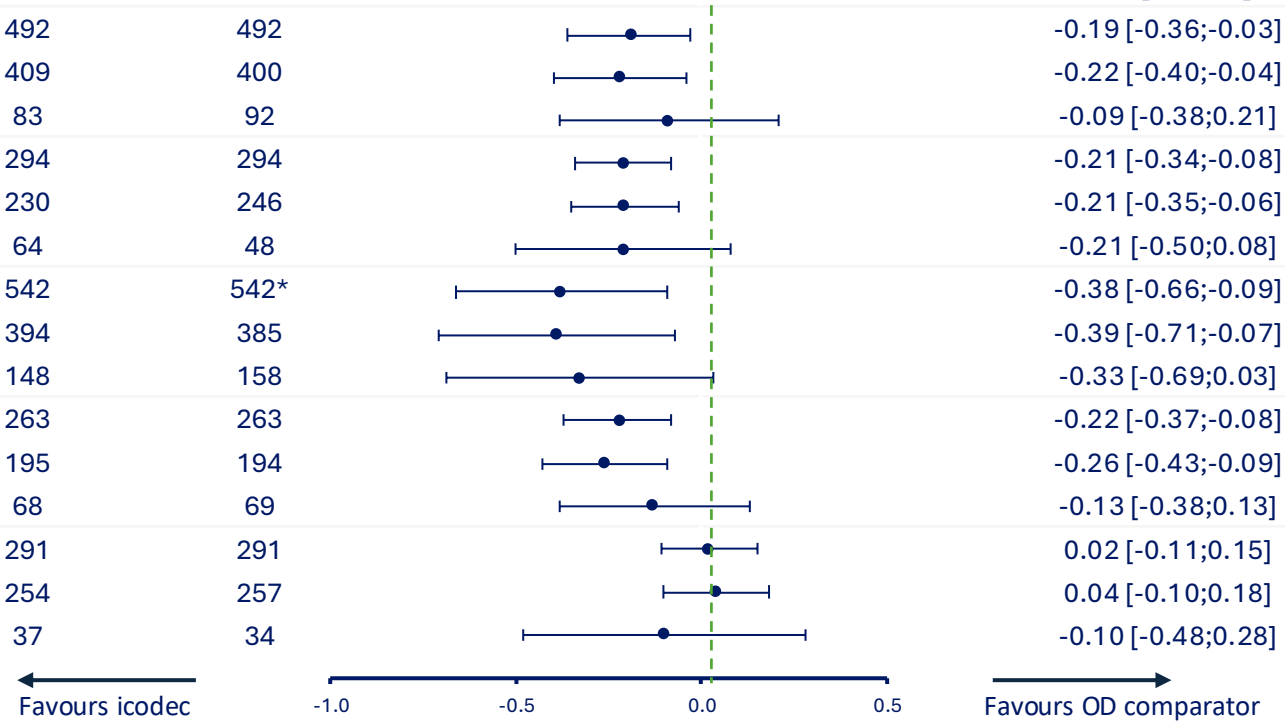
[a]ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5: week 52. [b]Clinically significant hypoglycaemia (level 2): blood glucose level of <54 mg/dL, confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. $HbA_{1C}$, glycated haemoglobin; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Vilsbøll T et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 840-P.

# ETD in change in $HbA_{1C}$ from baseline to EOT

## Efficacy and hypoglycaemia outcomes in T2D according to baseline GLP-1RA use: ONWARDS 1–5

| | | Icodec | OD comparator | ETD [95% CI] | p-value |
|---|---|---|---|---|---|
| Insulin-naïve | **ONWARDS 1 total** | 492 | 492 | -0.19 [-0.36;-0.03] | |
| | No GLP-1RA use | 409 | 400 | -0.22 [-0.40;-0.04] | 0.41 |
| | GLP-1RA use | 83 | 92 | -0.09 [-0.38;0.21] | |
| | **ONWARDS 3 total** | 294 | 294 | -0.21 [-0.34;-0.08] | |
| | No GLP-1RA use | 230 | 246 | -0.21 [-0.35;-0.06] | 0.98 |
| | GLP-1RA use | 64 | 48 | -0.21 [-0.50;0.08] | |
| | **ONWARDS 5 total** | 542 | 542* | -0.38 [-0.66;-0.09] | |
| | No GLP-1RA use | 394 | 385 | -0.39 [-0.71;-0.07] | 0.76 |
| | GLP-1RA use | 148 | 158 | -0.33 [-0.69;0.03] | |
| Insulin-experienced | **ONWARDS 2 (basal switch) total** | 263 | 263 | -0.22 [-0.37;-0.08] | |
| | No GLP-1RA use | 195 | 194 | -0.26 [-0.43;-0.09] | 0.39 |
| | GLP-1RA use | 68 | 69 | -0.13 [-0.38;0.13] | |
| | **ONWARDS 4 (basal/bolus switch) total** | 291 | 291 | 0.02 [-0.11;0.15] | |
| | No GLP-1RA use | 254 | 257 | 0.04 [-0.10;0.18] | 0.50 |
| | GLP-1RA use | 37 | 34 | -0.10 [-0.48;0.28] | |




Across all trials, participants receiving icodec versus OD comparators had larger or similar $HbA_{1c}$ reductions from baseline to EOT irrespective of GLP-1RA use; there was no statistically significant treatment by GLP-1RA subgroup interaction in $HbA_{1c}$ changes

Participants were not stratified according to their baseline GLP-1RA use. Change in $HbA_{1c}$ from baseline to planned EOT was analysed using an ANCOVA model, with treatment, region, treatment by subgroup interactions and, if applicable, additional relevant factors as fixed factors and the baseline response as a covariate. Missing data were imputed using multiple imputation. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. ANCOVA, analysis of covariance; CI, confidence interval; EOT, end of treatment; ETD, estimated treatment difference; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; GLP-1RA, glucagon-like peptide-1 receptor agonist; $HbA_{1c}$, glycated haemoglobin; icodec, insulin icodec; OD, once-daily.

1. Vilsbøll T et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 840-P.

# Rates of clinically significant or severe hypoglycaemia

## Efficacy and hypoglycaemia outcomes in T2D according to baseline GLP-1RA use: ONWARDS 1–5

| Trial | | Participants with/without GLP-1RA use, n | With GLP-1RA use at baseline | | | | Without GLP-1RA use at baseline | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Icodec | | OD comparator | | Icodec | | OD comparator | |
| | | | n (%) | E (R) | n (%) | E (R) | n (%) | E (R) | n (%) | E (R) |
| **Clinically significant or severe hypoglycaemia[a], events/PYE** | | | | | | | | | | |
| Insulin-naive participants | ONWARDS 1 | Icodec: 83/409<br>OD comparator: 92/400 | 11 (13.3) | 22 (0.17) | 10 (10.9) | 13 (0.09) | 50 (12.2) | 205 (0.32) | 60 (15.0) | 108 (0.17) |
| | ONWARDS 3 | Icodec: 64/230<br>OD comparator: 48/246 | 7 (10.9) | 9 (0.24) | 3 (6.2) | 4 (0.14) | 19 (8.3) | 44 (0.33) | 15 (6.1) | 21 (0.15) |
| | ONWARDS 5 | Icodec: 148/394<br>OD comparator: 158/385 | 15 (10.1) | 17 (0.11) | 9 (5.7) | 12 (0.07) | 49 (12.4) | 87 (0.22) | 36 (9.4) | 69 (0.17) |
| Insulin-experienced participants | ONWARDS 2 | Icodec: 68/195<br>OD comparator: 69/194 | 9 (13.2) | 11 (0.27) | 3 (4.3) | 4 (0.10) | 28 (14.4) | 102 (0.89) | 16 (8.2) | 38 (0.34) |
| | ONWARDS 4 | Icodec: 37/254<br>OD comparator: 34/257 | 21 (56.8) | 122 (5.65) | 13 (38.2) | 62 (3.12) | 129 (50.8) | 822 (5.64) | 149 (58.0) | 876 (5.96) |

- Overall rates of clinically significant or severe hypoglycaemia were low across treatment arms in ONWARDS 1, 2, 3 and 5, irrespective of GLP-1RA use (<1 event per PYE)
- In ONWARDS 4, rates of clinically significant or severe hypoglycaemia were similar between GLP-1RA users and non-users in the icodec arm

Clinically significant hypoglycaemia (level 2): blood glucose level of <54 mg/dL, confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300.

[a]Hypoglycaemic episodes that occurred during the on-treatment period (onset date on or after the first dose of trial product and no later than the first date of the follow-up visit, the last date on-trial product +5 weeks for OD insulin and +6 weeks for OW insulin or the end date for the in-trial period).

Degludec, insulin degludec; E, number of hypoglycaemic episodes; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; GLP-1RA, glucagon-like peptide-1 receptor agonist; icodec, insulin icodec; n, number of participants; OD, once-daily; OW, once-weekly; PYE, patient-year of exposure; R, rate of hypoglycaemia (number of episodes/PYE).

1. Vilsbøll T et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 840-P.

# Summary

## Efficacy and hypoglycaemia outcomes in T2D according to baseline GLP-1RA use: ONWARDS 1–5

Overall, the efficacy and safety of OW icodec versus OD comparators were generally consistent among individuals with T2D, regardless of GLP-1RA treatment at baseline

Across GLP-1RA subgroups, there were no statistically significant treatment by GLP-1RA subgroup interaction effects with respect to change in $HbA_{1C}$ from baseline to EOT

Rates (events per PYE) of clinically significant or severe hypoglycaemia were low across the treatment arms of ONWARDS 1, 2, 3 and 5, with an overall numerically lower rate in GLP-1RA users than non-users across all trials (except in ONWARDS 4)

- In ONWARDS 4, the icodec arm had a similar rate of clinically significant or severe hypoglycaemia in GLP-1RA users and non-users

There were no statistically significant treatment by GLP-1RA subgroup interaction effects with respect to the proportion of participants who achieved $HbA_{1C}$ targets without hypoglycaemia and change in body weight from baseline to EOT

EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; $HbA_{1C}$, glycated haemoglobin; icodec, insulin icodec; OD, once-daily; OW, once-weekly; PYE, patient-year of exposure; T2D, type 2 diabetes.

1. Vilsbøll T et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 840-P.

# ASSOCIAZIONI CON SGLT-2

# *Efficacy and hypoglycaemia outcomes in T2D according to **baseline SGLT2i use**: ONWARDS 1–5*

Post-hoc analyses

**Aim**: This post-hoc analysis of the ONWARDS 1–5 trials assessed the treatment effects of OW icodec compared with OD basal insulin comparators according to baseline SGLT2i use in individuals with T2D

- Participants treated with pre-trial SGLT2is were included in the trial, but they were not stratified by baseline SGLT2i use upon randomisation[a]
- SGLT2i treatments were continued throughout the trial as recommended by the trial protocols

**Treatment outcomes assessed by trial according to SGLT2i use at baseline**

- Estimated change in $HbA_{1C}$ from baseline to EOT[b]
- Observed rates of clinically significant or severe hypoglycaemia[c]
- Estimated proportion of participants achieving $HbA_{1C}$ <7% at EOT without clinically significant or severe hypoglycaemic episodes in the previous 12 weeks
- Estimated mean weekly basal insulin dose during the last 2 weeks of treatment
- Estimated change in body weight from baseline to EOT

[a]In ONWARDS 4, participants also received bolus insulin aspart injections 2–4 times daily.
EOT, end of treatment; $HbA_{1C}$, glycated haemoglobin; Icodec, insulin icodec; OD, once-daily; OW, once-weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.
1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.

# Baseline characteristics in SGLT2i users and non-users in ONWARDS 1–5

## Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5

Of the 3765 participants in the ONWARDS 1–5 trials, 36.9% were treated with SGLT2i (icodec: 37.8%; OD comparator: 36.0%)

In all trials, baseline characteristics (age, BMI, sex, diabetes duration) were broadly similar between treatment arms irrespective of baseline SGLT2i use

In all trials, except for ONWARDS 2, baseline $HbA_{1c}$ was slightly lower in SGLT2i users compared with non-users between treatment arms

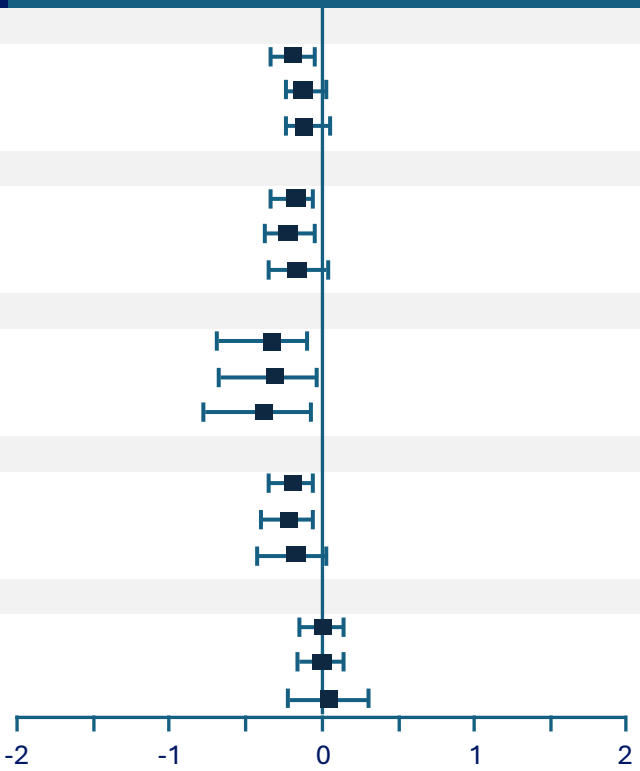
BMI, body mass index; $HbA_{1c}$, glycated haemoglobin; icodec, insulin icodec; OD, once-daily; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.

# ETD change in $HbA_{1c}$ from baseline to EOT

Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5

| | Study | Proportion of participants, %: Icodec | Proportion of participants, %: OD Comparator | ETD (95% CI), 5-points | *p* value for test of subgroup interaction |
|---|---|---|---|---|---|
| Insulin-naïve participants | **ONWARDS 1** | | | | |
| | Total | | | -0.19 (-0.36, -0.03) | |
| | No SGLT2i use | 62.0 | 65.0 | -0.13 (-0.27, 0.01) | 0.72 |
| | SGLT2i us | 38.0 | 35.0 | -0.09 (-0.26, 0.08) | |
| | **ONWARDS 3** | | | | |
| | Total | | | -0.21 (-0.34, -0.08) | |
| | No SGLT2i use | 59.5 | 67.7 | -0.24 (-0.40, -0.07) | 0.63 |
| | SGLT2i use | 41.5 | 32.3 | -0.17 (-0.38, 0.04) | |
| | **ONWARDS 5** | | | | |
| | Total | | | -0.38 (-0.66, -0.09) | |
| | No SGLT2i use | 56.8 | 55.8 | -0.33 (-0.65, -0.01) | 0.58 |
| | SGLT2i use | 43.2 | 44.2 | -0.43 (-0.78, -0.08) | |
| Insulin-experienced participants | **ONWARDS 2 (basal only)** | | | | |
| | Total | | | -0.22 (-0.37, -0.08) | |
| | No SGLT2i use | 66.2 | 68.1 | -0.23 (-0.41, -0.06) | 0.83 |
| | SGLT2i use | 33.8 | 31.9 | -0.20 (-0.45, 0.04) | |
| | **ONWARDS 4 (basal-bolus)** | | | | |
| | Total | | | 0.02 (-0.11, 0.15) | |
| | No SGLT2i use | 71.8 | 70.4 | 0.01 (-0.14, 0.17) | 0.88 |
| | SGLT2i use | 28.2 | 29.6 | 0.04 (-0.21, 0.28) | |



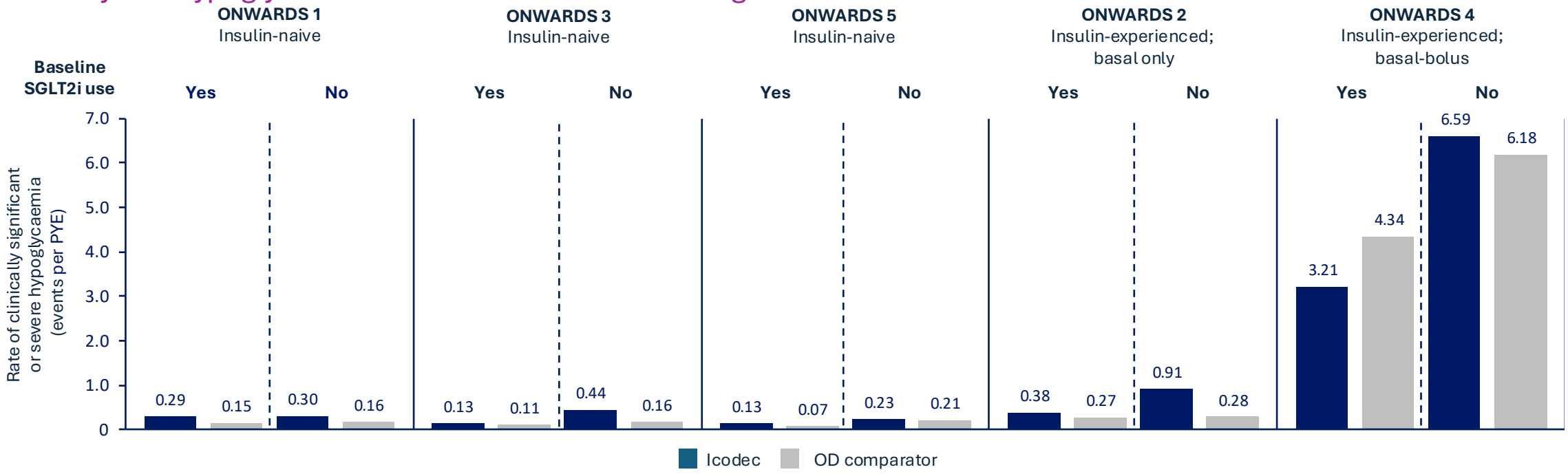

Across all five trials, participants receiving icodec compared with OD comparators had larger or similar $HbA_{1c}$ reductions from baseline to EOT irrespective of SGLT2i use; there was no statistically significant treatment by SGLT2i subgroup interaction in $HbA_{1c}$ changes

EOT: ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52. ETD: icodec – OD comparator. Participants were not stratified according to their baseline SGLT2i use. Change in HbA1c from baseline to planned EOT was analysed using an ANCOVA model, with treatment, region, treatment by subgroup interactions and, if applicable, additional relevant factors as fixed factors and the baseline response as a covariate. Missing data were imputed using multiple imputation. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. ANCOVA, analysis of covariance; CI, confidence interval; degludec, insulin degludec; EOT, end of treatment; ETD, estimated treatment difference; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; $HbA_{1c}$, glycated haemoglobin; icodec, insulin icodec; OD, once-daily; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.

# Clinically significant or severe hypoglycaemia

## Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5




- Overall rates of clinically significant or severe hypoglycaemia were low between treatment arms in ONWARDS 1, 2, 3 and 5, irrespective of SGLT2i use (<1 event per PYE)
- In ONWARDS 4, the rate of clinically significant or severe hypoglycaemia was comparable or numerically lower with icodec compared with the OD comparator across subgroups

Clinically significant hypoglycaemia (level 2): blood glucose level of <3.0 mmol/L, confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. Graph shows the hypoglycaemic episodes that occurred during the on-treatment period (onset date on or after the first dose of trial product and no later than the first date of the follow-up visit, the last date on-trial product +5 weeks for OD insulin and +6 weeks for OW insulin or the end date for the in-trial period). Degludec, insulin degludec; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodec, insulin icodec; OD, once-daily; OW, once-weekly; PYE, patient-year of exposure; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.

# Summary

## Efficacy and hypoglycaemia outcomes in T2D according to baseline SGLT2i use: ONWARDS 1–5

Overall, the efficacy and hypoglycaemia outcomes with OW icodec compared with OD comparators were generally consistent among individuals with T2D, regardless of SGLT2i treatment at baseline

Across the SGLT2i subgroups, there was no statistically significant treatment by SGLT2i subgroup interaction with respect to change in $HbA_{1c}$ from baseline to EOT

Rates of clinically significant or severe hypoglycaemia were low across the treatment arms of ONWARDS 1, 2, 3 and 5, regardless of SGLT2i use at baseline; in ONWARDS 4, the rate was comparable or numerically lower with icodec compared with OD comparator across subgroups

There were no statistically significant treatment by SGLT2i subgroup interaction effects with respect to the achievement of HbA1c targets without clinically significant or severe hypoglycaemia (in all trials), and in the insulin dose and the change in body weight in ONWARDS 1–4

In ONWARDS 5, statistically significant treatment by SGLT2i subgroup interactions were observed for icodec compared with OD comparators in weekly basal insulin dose and change in body weight; specifically, the weight change was most pronounced with icodec compared with OD comparators in SGLT2i users

Clinically significant hypoglycaemia (level 2): blood glucose level of <3.0 mmol/L, confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery.
EOT, end of treatment; $HbA_{1c}$, glycated haemoglobin; insulin icodec; OD, once-daily; OW, once-weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.

1. Goldenberg R et al. EASD 60th Annual Meeting, September 9–13, 2024. Madrid, Spain and online.

# ASSOCIAZIONI CON CKD

# *Efficacy and hypoglycaemia outcomes in individuals with T2D **by kidney function**: ONWARDS 1–5*

Post-hoc analyses

**Aim:** This post-hoc analysis of ONWARDS 1–5 assessed the efficacy and hypoglycaemia outcomes with once-weekly icodec versus OD basal insulin comparators in insulin-naive and insulin-experienced adults with T2D by kidney function subgroup

**Methods**

- ONWARDS 1–5 were multinational, multicenter trials that included insulin-naive (ONWARDS 1, 3 and 5) and insulin-experienced (ONWARDS 2 and 4) adults (aged ≥18 years) with T2D
- Severe kidney function impairment (eGFR <30 mL/min/1.73 m2 at screening) was an exclusion criterion for ONWARDS 1–4; in ONWARDS 5, there were no exclusion criteria for eGFR
- In ONWARDS 5, icodec titration was guided by a dosing guide app; OD comparator doses were titrated at the investigator's discretion as per standard clinical practice

[a]In ONWARDS 4 (basal-bolus trial), participants also received 2–4 daily injections of insulin aspart.
eGFR, estimated glomerular filtration rate; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodec, insulin icodec; OD, once-daily; T2D, type 2 diabetes.
1. Rossing P et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 826-P.

# Post-hoc analysis and trial participants

## Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5

ONWARDS 1–5 treatment outcomes were analysed by trial according to kidney function subgroup to assess:

- Change in $HbA_{1C}$[a]
- Observed rates of combined clinically significant or severe hypoglycaemia[b]
- Proportion of participants achieving an $HbA_{1C}$ <7% without clinically significant or severe hypoglycaemia[c]
- Mean weekly total insulin dose[d]

**Kidney function subgroups were based on eGFR at screening**

**Of the 3765 participants in ONWARDS 1–5, 3763 had eGFR measurements at screening and were included in this analysis:**

**Normal kidney function**
eGFR ≥90
n=1875 (49.8%)

**Mild kidney function impairment**
eGFR 60–<90
n=1450 (38.5%)

**Moderate kidney function impairment**
eGFR 30–<60
n=430 (11.4%)

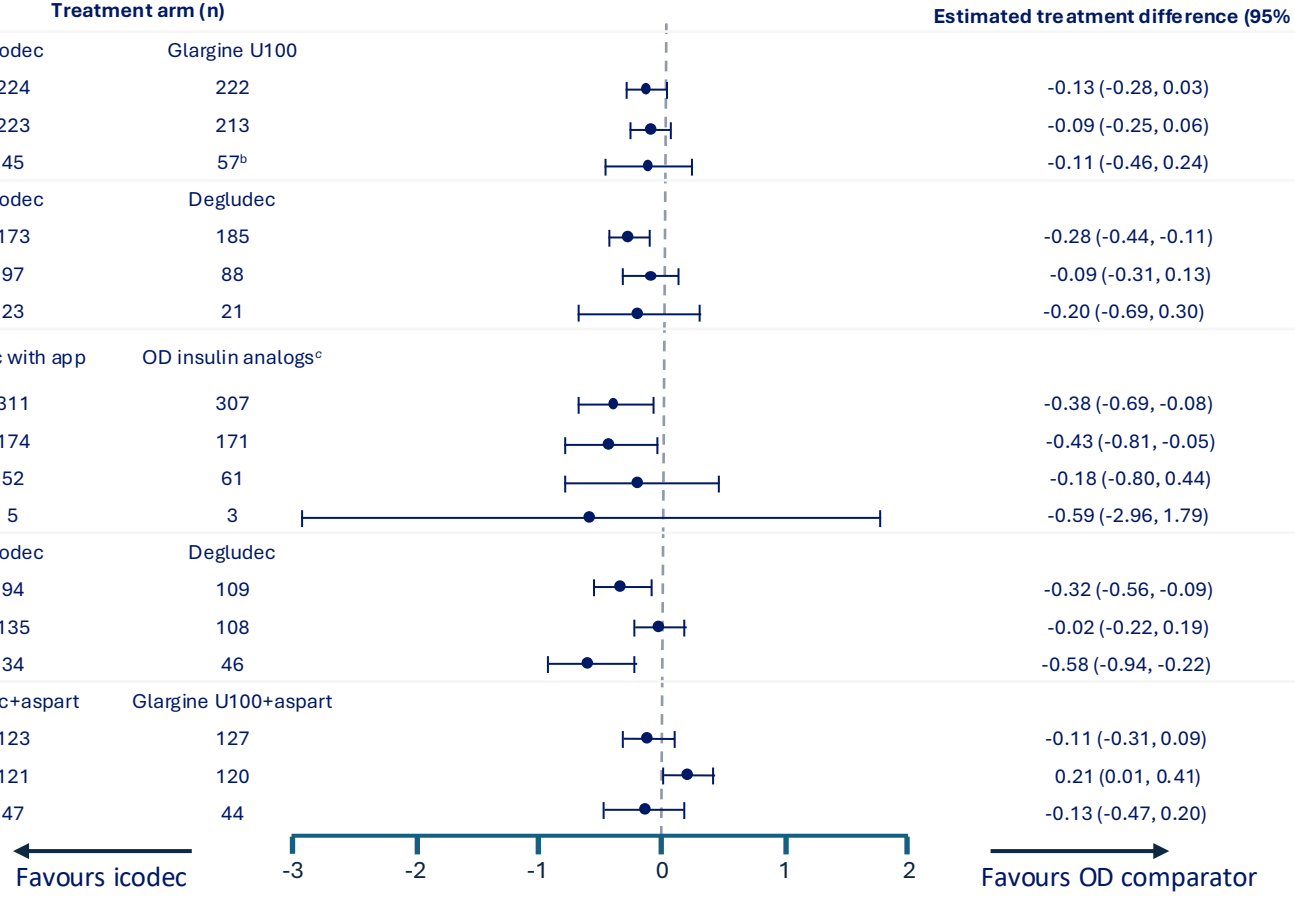
**Severe kidney function impairment**
eGFR <30
n=8 (0.2%)

All eGFR values are presented in mL/min/1.73m$^2$. Clinically significant hypoglycaemia: blood glucose level of <54 mg/dL, confirmed by blood glucose meter. Severe hypoglycaemia: hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. [a]From baseline to the planned EOT (ONWARDS 1: week 78; ONWARDS 2–4: week 26; ONWARDS 5: week 52). [b]From baseline to week 83 (ONWARDS 1), week 31 (ONWARDS 2–4), or week 57 (ONWARDS 5). [c]Proportion of participants achieving an $HbA_{1C}$ <7% at EOT without clinically significant or severe hypoglycaemia in the previous 12 weeks. [d]During the last 2 weeks of treatment.
eGFR, estimated glomerular filtration rate; EOT, end of treatment; $HbA_{1C}$, glycated haemoglobin.
1. Rossing P et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 826-P.

# Change in $HbA_{1C}$ from baseline to planned EOT

## Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5

| | | Treatment arm (n) | | Estimated treatment difference (95% CI) | *p*-value[a] |
|---|---|---|---|---|---|
| Insulin-naïve | **ONWARDS** | Icodec | Glargine U100 | | |
| | Normal kidney function (eGFR ≥90) | 224 | 222 | -0.13 (-0.28, 0.03) | |
| | Mild kidney function impairment (eGFR 60-<90) | 223 | 213 | -0.09 (-0.25, 0.06) | 0.9593 |
| | Moderate or severe kidney function impairment (eGFR <60) | 45 | 57[b] | -0.11 (-0.46, 0.24) | |
| | **ONWARDS 3** | Icodec | Degludec | | |
| | Normal kidney function (eGFR ≥90) | 173 | 185 | -0.28 (-0.44, -0.11) | |
| | Mild kidney function impairment (eGFR 60-<90) | 97 | 88 | -0.09 (-0.31, 0.13) | 0.4317 |
| | Moderate kidney function impairment (eGFR -<60) | 23 | 21 | -0.20 (-0.69, 0.30) | |
| | **ONWARDS 5** | Icodec with app | OD insulin analogs[c] | | |
| | Normal kidney function (eGFR ≥90) | 311 | 307 | -0.38 (-0.69, -0.08) | |
| | Mild kidney function impairment (eGFR 60-<90) | 174 | 171 | -0.43 (-0.81, -0.05) | 0.8955 |
| | Moderate kidney function impairment (eGFR -<60) | 52 | 61 | -0.18 (-0.80, 0.44) | |
| | Severe kidney function impairment (eGFR <30) | 5 | 3 | -0.59 (-2.96, 1.79) | |
| Insulin-experienced | **ONWARDS 2 (basal switch)** | Icodec | Degludec | | |
| | Normal kidney function (eGFR ≥90) | 94 | 109 | -0.32 (-0.56, -0.09) | |
| | Mild kidney function impairment (eGFR 60-<90) | 135 | 108 | -0.02 (-0.22, 0.19) | **0.0138** |
| | Moderate kidney function impairment (eGFR -<60) | 34 | 46 | -0.58 (-0.94, -0.22) | |
| | **ONWARDS 4 (basal/bolus switch)** | Icodec+aspart | Glargine U100+aspart | | |
| | Normal kidney function (eGFR ≥90) | 123 | 127 | -0.11 (-0.31, 0.09) | |
| | Mild kidney function impairment (eGFR 60-<90) | 121 | 120 | 0.21 (0.01, 0.41) | **0.0493** |
| | Moderate kidney function impairment (eGFR 30-<60) | 47 | 44 | -0.13 (-0.47, 0.20) | |




For two individuals, eGFR was not measured at screening; all eGFR values are presented in mL/min/1.73m$^2$. Change in $HbA_{1C}$ from baseline to planned EOT was analysed using an ANCOVA, with treatment, region, treatment by subgroup interactions and, if applicable, additional relevant factors as fixed factors, and the baseline response as a covariate. Bold values denote statistical significance at the p<0.05 level.

[a]Two-sided p value for the test of no treatment by kidney function subgroup interactions.

[b]Includes moderate kidney impairment (n=56) and severe kidney impairment (n=1). In ONWARDS 1, one participant with severe kidney impairment was erroneously randomised to receive treatment.

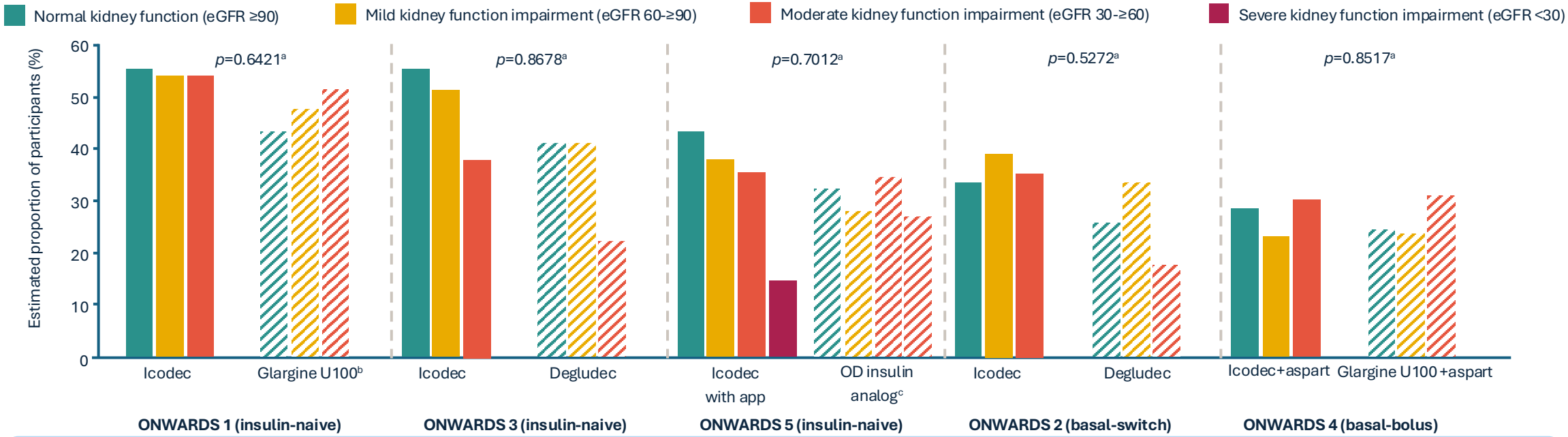
[c]In ONWARDS 5, participants in the comparator arm received once-daily degludec, glargine U100, or glargine U300 at the investigators' discretion.

ANCOVA, analysis of covariance; aspart, insulin aspart; degludec, insulin degludec; eGFR, estimated glomerular filtration rate; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargline U300; icodec, insulin icodec; OD, once-daily.

1. Rossing P et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 826-P.

# Proportion of participants who achieved $HbA_{1C}$ <7% without clinically significant or severe hypoglycaemia

## Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5




Across trials, there were no statistically significant treatment interactions by kidney function subgroup for the composite endpoint (all $p>0.05$)

For two individuals, eGFR was not measured at screening; all eGFR values are presented in mL/min/1.73m$^2$. In the severe kidney function impairment subgroup of ONWARDS 5, one of five participants receiving icodec with app and one of three participants receiving an OD comparator achieved $HbA_{1C}$ <7% at EOT without clinically significant or severe hypoglycaemia. Clinically significant hypoglycaemia: blood glucose level of <54 mg/dL, confirmed by blood glucose meter. Severe hypoglycaemia: hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. The composite endpoint was analysed using a logistic regression model with log-link function. Treatment, region, and, if applicable, additional relevant factors were used as fixed factors, and the baseline $HbA_{1C}$ value as covariate. Missing $HbA_{1C}$ values were imputed using multiple imputation.

[a]p value for treatment by subgroup interaction.

[b]In ONWARDS 1, one participant with severe kidney impairment was erroneously randomised to receive treatment and included in the moderate kidney function impairment subgroup for the purpose of this analysis.

[c]In ONWARDS 5, participants in the comparator arm received once-daily degludec, glargine U100, or glargine U300 at the investigators' discretion.

Aspart, insulin aspart; degludec, insulin degludec; eGFR, estimated glomerular filtration rate; glargine U100, insulin glargine U100; $HbA_{1C}$, glycated haemoglobin; icodec, insulin icodec; OD, once-daily.

1. Rossing P et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 826-P.

# Summary

## Efficacy and hypoglycaemia outcomes in individuals with T2D by kidney function: ONWARDS 1–5

The efficacy and hypoglycaemia outcomes with once-weekly icodec versus OD comparators were generally consistent among insulin-naive and insulin-experienced adults with T2D, regardless of kidney function

Irrespective of kidney function, overall rates of combined clinically significant or severe hypoglycaemia were comparable between subgroups

Achievement of $HbA_{1C}$ <7% at EOT without clinically significant or severe hypoglycaemia with icodec was similar to or higher than with OD comparators in participants with normal kidney function, or with mild or moderate kidney function impairment (although, across trials, no statistically significant treatment interactions by kidney function subgroup were observed), and consistent with the overall results of the ONWARDS program

EOT, end of treatment; $HbA_{1C}$, glycated haemoglobin; OD, once-daily; T2D, type 2 diabetes.

1. Rossing P et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 826-P.

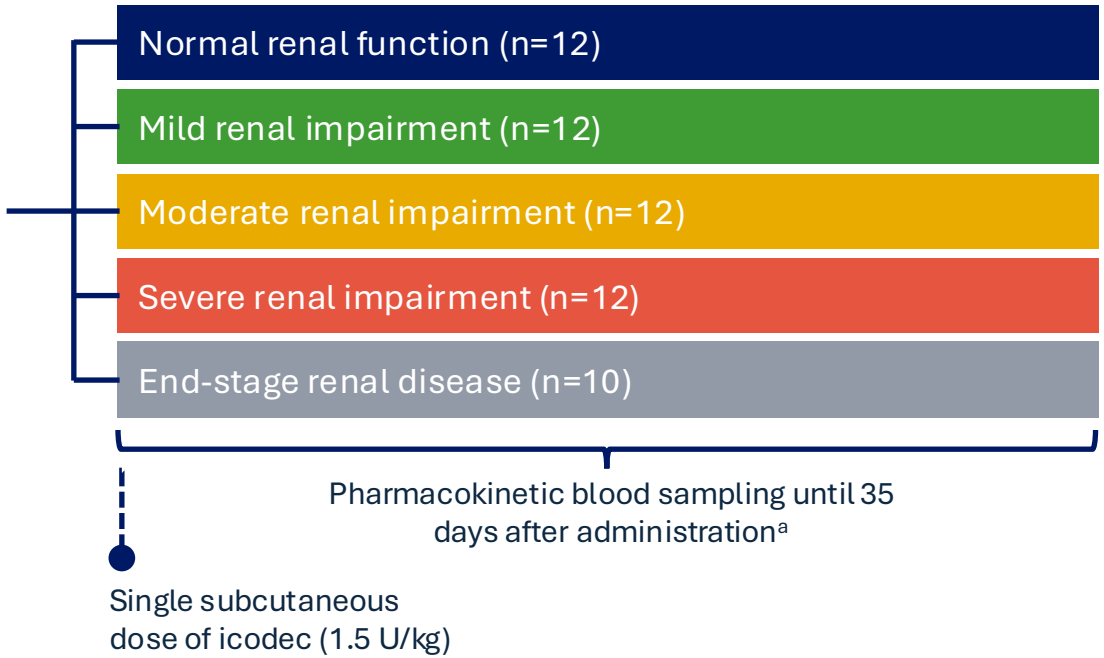
# The effect of various degrees of renal impairment on the pharmacokinetic characteristics of once-weekly insulin icodec

## Participants

- 58 individuals allocated to five groups based on renal function
- Individuals with renal impairment:
  - Diagnosis of chronic kidney disease
  - mGFR of 60 to <90 mL/min (mild renal impairment), 30 to <60 mL/min (moderate) or <30 mL/min not requiring dialysis (severe), or end-stage renal disease requiring hemodialysis
- Individuals with normal renal function:
  - Generally healthy
  - mGFR ≥90 mL/min

## Objective:

- To investigate if the pharmacokinetic characteristics of insulin icodec are affected by renal impairment

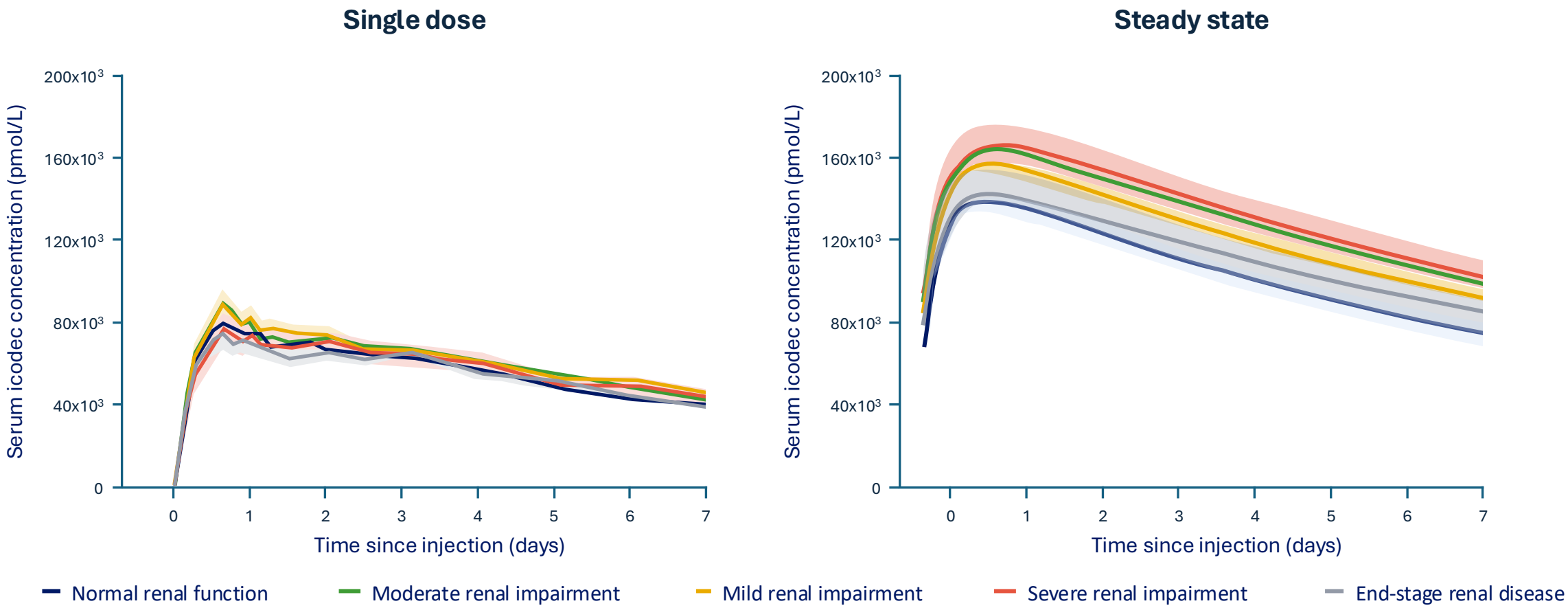



[a] In participants with end-stage renal disease, blood for pharmacokinetic analysis was also sampled during a hemodialysis session starting 138-164 hours after administration. Furthermore, in participants without end-stage renal disease, urine was collected before icodec administration and in the first 48 hours after dosing (i.e. around the expected maximum concentration) for analysis of any intact icodec extraction.

mGFR, measured glomerular filtration rate (using iohexol as an external marker).

1. Haahr H. et al, Clin Pharmacokinet 2024, DOI:10.1007/s40262-024-01375-2.

# Mean serum insulin icodec concentration during a dosing interval of one week




Insulin icodec dose: 1.5 U/kg. Simulation at steady state: Based on the observed serum icodec concentrations after a single dose, a one-compartment pharmacokinetic model was developed, consisting of parameters to describe absorption, distribution and clearance. Renal function group was included as a covariate on the clearance parameter. The estimated model parameters for each individual were used to simulate the steady-state serum icodec profiles.

1. Haahr H. et al, Clin Pharmacokinet 2024, DOI:10.1007/s40262-024-01375-2.

# ASSOCIAZIONI CON EPATOPATIA

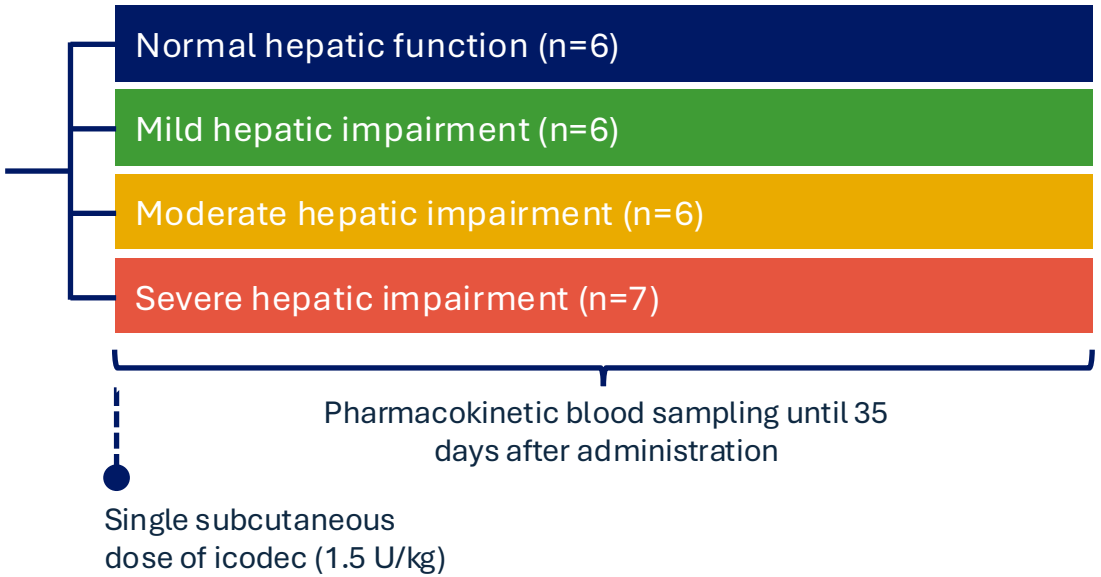
# The effect of various degrees of hepatic impairment on the pharmacokinetic characteristics of once-weekly insulin icodec

## Participants

- 25 individuals allocated to four groups based on hepatic function
- Individuals with hepatic impairment:
  - Child–Pugh Classification[1]
    used to allocate into
    mild (class A; 5–6 points), moderate (class B; 7–9 points) or severe
    (class C; 10–15 points)
- Individuals with normal hepatic function:
  - Age- and body weight-matched to the groups of hepatic impairment

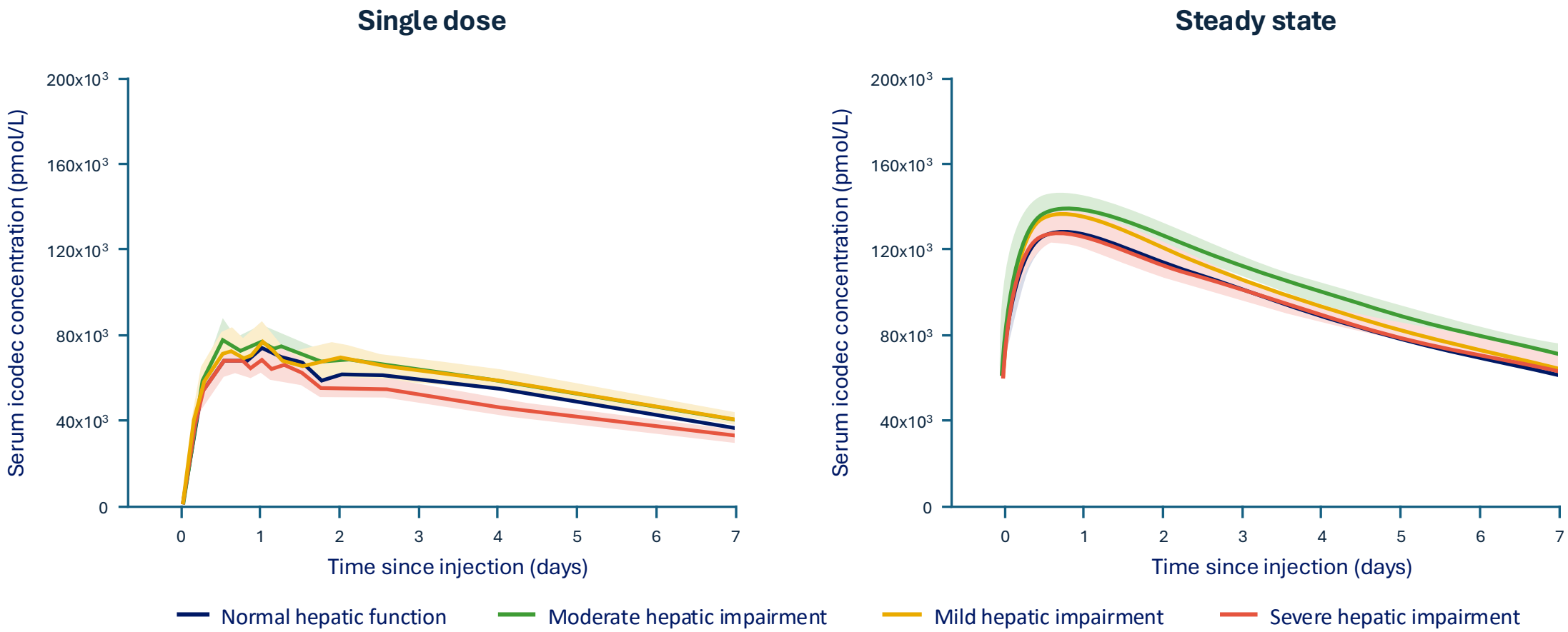
## Objective:

- To investigate if the pharmacokinetic characteristics of insulin icodec are affected by hepatic impairment




1. Pugh RN et al. Br J Surg 1973;60:646–9; 2. Haahr H. et al, Clin Pharmacokinet 2024, DOI:10.1007/s40262-024-01375-2.

# Mean serum insulin icodec concentration during a dosing interval of one week




Insulin icodec dose: 1.5 U/kg.
Simulation at steady state: Based on the observed serum icodec concentrations after a single dose, a one-compartment pharmacokinetic model was developed, consisting of parameters to describe absorption, distribution and clearance. Hepatic function group was included as a covariate on the clearance parameter. The estimated model parameters for each individual were used to simulate the steady-state serum icodec profiles.

1. Haahr H. et al, Clin Pharmacokinet 2024, DOI:10.1007/s40262-024-01375-2.

# ATTIVITA’ FISICA

# *Icodec and **physical activity-related hypoglycaemia**: insights from the ONWARDS 1–5 trials*

Post-hoc analyses

**Aim**: To assess the proportion and incidence of physical activity-related hypoglycaemic episodes, based on self-reported data, in adults with T2D in ONWARDS 1–5

**Methods**: ONWARDS 1–5 participants who reported hypoglycaemic episodes were asked whether each episode occurred in relation to physical activity

**In this post-hoc analysis the following were evaluated the:**

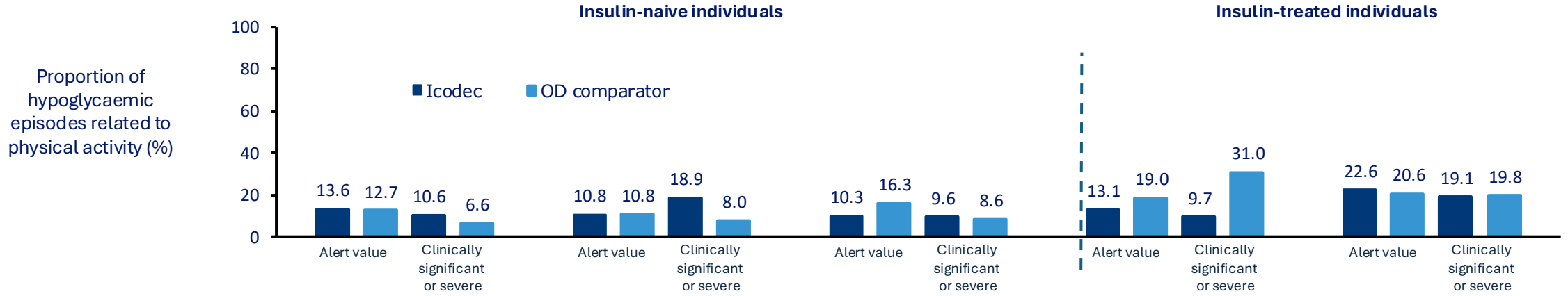
- Proportion of hypoglycaemic episodes that were related to physical activity
- Incidence of physical activity-related clinically significant or severe hypoglycaemia
- Proportion of clinically significant or severe hypoglycaemic episodes that were related to physical activity with at least one clinically significant or severe hypoglycaemic episode in the following 24 hours

T2D, type 2 diabetes.

1. Riddell MC et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 830-P.

# Proportion of hypoglycaemic episodes related to physical activity during the on-treatment period

## Icodec and physical activity-related hypoglycaemia: insights from ONWARDS 1–5



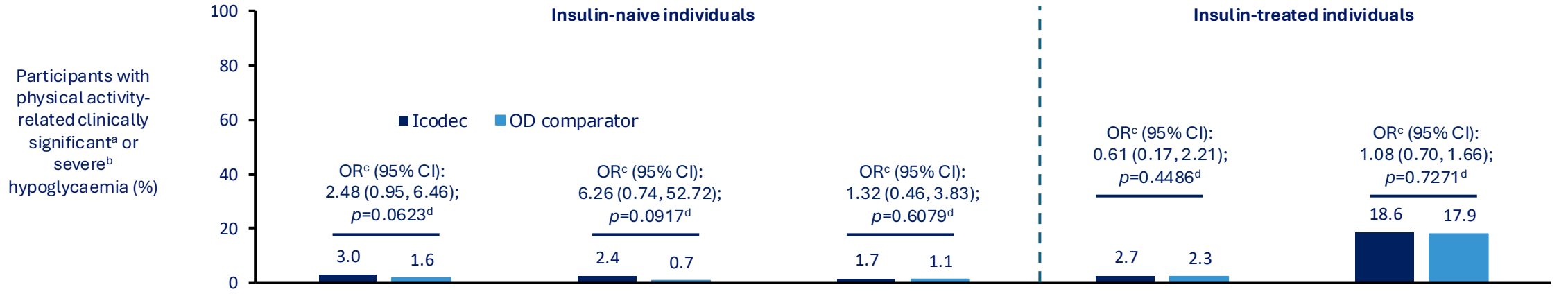

| Number of physical activity-related episodes/ total number of episodes | ONWARDS 1 (78-week trial) | | ONWARDS 3 (26-week trial) | | ONWARDS 5 (52-week trial with RWE) | | ONWARDS 2 (26-week trial) | | ONWARDS 4 (26-week trial) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Icodec | Glargine U100 | Icodec | Degludec | Icodec with dosing guide app | OD analogs[a] | Icodec | Degludec | Icodec + aspart | Glargine U100 + aspart |
| Hypoglycaemia alert value[b] | 314/2308 | 136/1067 | 43/400 | 20/185 | 106/1028 | 139/851 | 158/1209 | 112/589 | 1191/5264 | 853/4145 |
| Clinically significant hypoglycaemia[c] | 23/226 | 8/114 | 10/53 | 2/23 | 10/104 | 7/76 | 11/113 | 13/41 | 180/937 | 186/935 |
| Severe hypoglycaemia[d] | 1/1 | 0/7 | 0/0 | 0/2 | 0/0 | 0/5 | 0/0 | 0/1 | 0/7 | 0/3 |

There were no consistent differences in the proportions of physical activity-related hypoglycaemic episodes compared with the total number of hypoglycaemic episodes with icodec versus OD comparators

On-treatment period: onset date on or after the first dose of trial product and no later than the first date of the follow-up visit, the last date on-trial product +5 weeks for OD insulin and +6 weeks for once-weekly insulin or the end date for the in-trial period.
[a]The choice of the OD analog (degludec, glargine U100 or glargine U300) was made at the investigators' discretion. [b]Hypoglycaemia alert value: blood glucose value <70 mg/dL (<3.9 mmol/L) but ≥54mg/dL (≥3.0 mmol/L), confirmed by blood glucose meter. [c]Clinically significant hypoglycaemia: blood glucose value <54 mg/dL (<3.0 mmol/L), confirmed by blood glucose meter. [d]Severe hypoglycaemia: hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
OD, once-daily; RWE, real-world elements.
1. Riddell MC et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 830-P.

# Observed incidence of clinically significant or severe hypoglycaemia related to physical activity during the on-treatment period

## Icodec and physical activity-related hypoglycaemia: insights from ONWARDS 1–5




| | ONWARDS 1 (78-week trial) | | ONWARDS 3 (26-week trial) | | ONWARDS 5 (52-week trial with RWE) | | ONWARDS 2 (26-week trial) | | ONWARDS 4 (26-week trial) | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Number of physical activity-related episodes/ total number of episodes** | Icodec | Glargine U100 | Icodec | Degludec | Icodec with dosing guide app | OD analogs[a] | Icodec | Degludec | Icodec + aspart | Glargine U100 + aspart |
| Number of participants (full analysis set) | 492 | 492 | 294 | 294 | 542 | 543 | 263 | 263 | 291 | 291 |

There were no statistically significant differences in the odds of experiencing a physical activity-related clinically significant or severe hypoglycaemic episode with icodec versus OD comparators

The incidence of hypoglycaemia was analysed using a binary logistic regression model (logit link) with treatment, region, sulfonylurea/glinides use (ONWARDS 3) and personal continuous glucose monitoring device use (ONWARDS 2 and 4) as fixed factors. Missing data were imputed using multiple imputations. On-treatment period: onset date on or after the first dose of trial product and no later than the first date of the follow-up visit, the last date on-trial product +5 weeks for OD insulin and +6 weeks for once-weekly insulin or the end date for the in-trial period.
[a]Clinically significant hypoglycaemia: blood glucose value <54 mg/dL (<3.0 mmol/L), confirmed by blood glucose meter. [b]Severe hypoglycaemia: hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. [c]Icodec/OD comparator. [d]Two-sided p value for the test of no treatment difference (no correction for multiplicity). [e]The choice of the OD analog (degludec, glargine U100 or glargine U300) was made at the investigators' discretion.
CI, confidence interval; OD, once-daily; OR, odds ratio; RWE, real world evidence.
1. Riddell MC et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 830-P.

# Proportion of clinically significant or severe hypoglycaemic episodes related to physical activity with at least one additional clinically significant or severe hypoglycaemic episode in the following 24 hours

## Icodec and physical activity-related hypoglycaemia: insights from ONWARDS 1–5

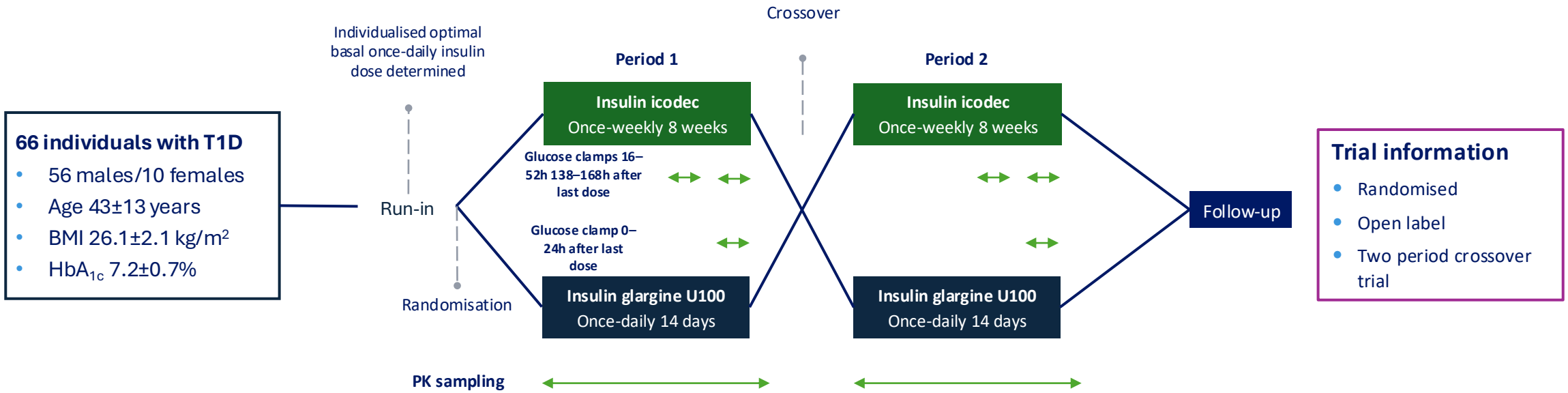
| Clinically significant[a] or severe[b] hypoglycaemic episodes related to physical activity (%) | Icodec | | OD comparator | |
|---|---|---|---|---|
| | Clinically significant hypoglycaemia | Severe hypoglycaemia | Clinically significant hypoglycaemia | Severe hypoglycaemia |
| ONWARDS 1 (basal initiation; 78-week trial) | 0 | 0 | 0 | 0 |
| ONWARDS 3 (basal initiation; 26-week trial) | 0 | 0 | 0 | 0 |
| ONWARDS 5 (basal initiation; 52-week trial with real-world elements) | 0 | 0 | 0 | 0 |
| ONWARDS 2 (basal switch; 26-week trial) | 27.3 | 0 | 0 | 0 |
| ONWARDS 4 (basal-bolus; 26-week trial) | 15.0 | 0 | 8.6 | 0 |

The frequency of recurrent clinically significant or severe hypoglycaemic episodes 24 hours after a physical activity-related clinically significant or severe hypoglycaemic episode was low, with no additional severe episodes reported in any participants across the trials

[a]Clinically significant hypoglycaemia: blood glucose value <54 mg/dL (<3.0 mmol/L), confirmed by blood glucose meter.
[b]Severe hypoglycaemia: hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
OD, once-daily.
1. Riddell MC et al. ADA 84th Scientific Sessions. June 21–24, 2024, Orlando Florida. 830-P.

# DMT1

# Once-weekly insulin icodec: pharmacokinetic and pharmacodynamic properties in T1D




## Trial objectives

- To investigate the pharmacokinetic and pharmacodynamic properties of icodec at steady state in individuals with T1D

## Methodology

- Run-in up to 10 weeks: Once-daily glargine U100, fasting SMPG target 4.4–7.2 mmol/L
- Individualised fixed doses of icodec and glargine U100 at equimolar total weekly doses (mean±SD 1.91±0.44 U/kg; range 1.1-3.3 U/kg)
- Insulin aspart as bolus insulin
- Automated glucose clamps after the last insulin dose (ClampArt; target blood glucose 6.7 mmol/L)
- PK-PD modelling to assess the glucose-lowering effect of icodec during a full one-week dosing interval

Wash-out period: 35-49 days following icodec treatment and 2-15 days following glargine U100 treatment.
PD, pharmacodynamic; PK, pharmacokinetic; SMPG, self-measured plasma glucose; T1D, type 1 diabetes.
1. Hövelmann U et al. *Diabetes Obes Metab*. 2024. DOI: 10.1111/dom.15510.

# Hypoglycaemia and other safety information

| | Icodec | Glargine U100 |
|---|---|---|
| Rate of overall clinically significant hypoglycaemic (episodes per PYE) | 32.8 | 23.9 |
| Rate of nocturnal clinically significant hypoglycaemic (episodes per PYE) | 5.4 | 4.4 |
| Duration of clinically significant hypoglycaemic episodes[a] (minutes) | 33±25 | 30±18 |

Icodec and glargine U100 were both **well tolerated** in this trial

[a]Data are mean±SD
One level 3 hypoglycaemic episode was reported during icodec treatment. The event occurred 4 days after the 4th weekly icodec dose. The participant remained conscious and showed no signs of disorientation. A relative supplied apple juice (which was the reason for the classification of the event as severe). The participant self-injected glucagon intramuscularly after SMPG values were still below 3.3 mmol/L (60 mg/dL) despite intake of carbohydrates, whereafter the hypoglycaemic episode was resolved after 51 min.
PYE, participant-years of exposure; SMPG, self-measured plasma glucose.
1. Hövelmann U et al. *Diabetes Obes Metab*. 2024. DOI: 10.1111/dom.15510.

# NEWS

AME News *Farmaci*

nr. 49 - mese 2025

**Capo-Redattore:** Chiara Sabbadin

**Redattori**: Silvia Briganti, Simona Censi, Carmela Coccaro, Sara De Vincentis, Rita Indirli, Pina Lardo, Alessandro Mondin, Lara Naletto, Valerio Renzelli



# NUOVA FORMULAZIONE PER L'INSULINA ICODEC

**Coordinatori**
Renato Cozzi & Patrizia Del Monte
**Editor**
Vincenzo Di Donna & Cecilia Motta

La determina AIFA 1310/2025 autorizza la prossima commercializzazione di una nuova formulazione di insulina Icodec (Awiqli®).

Accanto alla formulazione da 3 mL (700 U/mL in penna pre-riempita da 3 mL), per rispondere all'esigenza dei pazienti che devono somministrare meno di 175 U/settimana, **arriva la formulazione da 1.5 mL** (contiene 1050 U di insulina Icodec in luogo delle 2100 delle formulazioni da 3 mL).

Questa nuova formulazione consentirà di evitare eventuali sprechi di insulina nei soggetti che somministrano un quantitativo ridotto settimanale di unità di insulina. Infatti, dopo la prima apertura, **il medicinale può essere conservato al massimo per 12 settimane alla temperatura di 2-8°C.**

# CONCLUSIONI

- Meno iniezioni, meno aghi
- Minor rischio lipodistrofie
- Maggiore accettabilità da parte del paziente
- Maggior compliance con i care giver
- Maggiore aderenza alla terapia
- Possibilità di titolare con un minor consumo di strisce
- Meno ipoglicemie


GRAZIE PER
L'ATTENZIONE
memegenerator.net