un secolo di insulina: dove siamo arrivati e dove stiamo andando

Andrea Giaccari

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

TEAM DIABETE

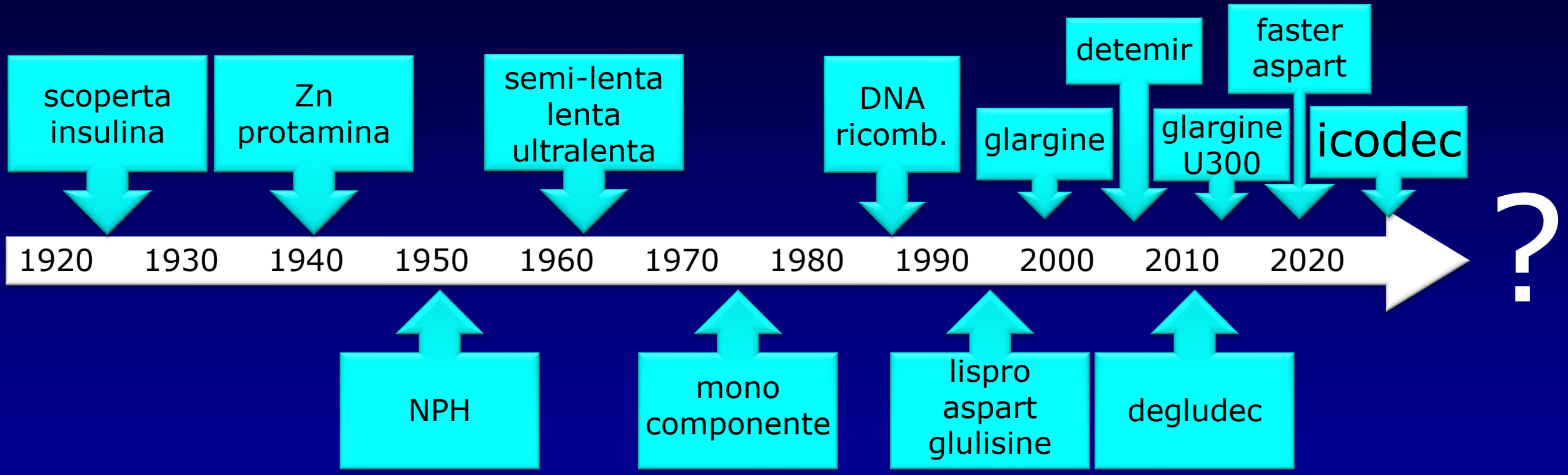
DICHIARAZIONE CONFLITTO D'INTERESSE DOCENTI

Il sottoscritto prof. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Astra Zeneca
- Lilly
- Novo-Nordisk
- Sanofi

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.).

un secolo di insulina



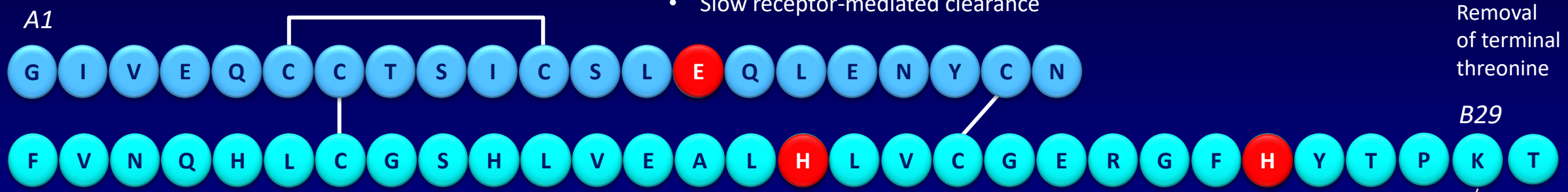
NPH, neutral protamine Hagedorn

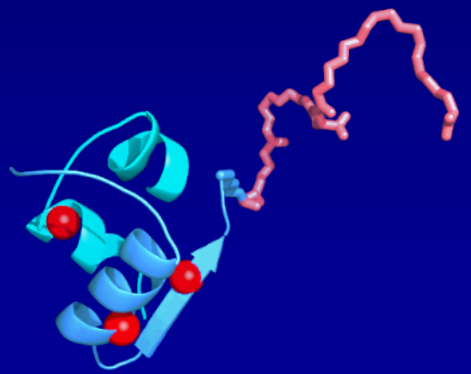
Adapted from Cahn *et al. Lancet Diabetes Endocrinol* 2015;3:638–52; Kim & Plosker. *Drugs* 2015;75:1679–86

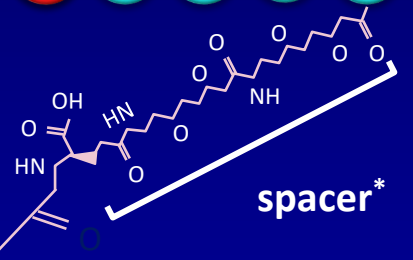
Icodec is designed to achieve a long half-life by changes to the human insulin molecule

Three amino acid substitutions

- Molecular stability
- Reduced enzymatic degradation
- Slow receptor-mediated clearance







C20 icosane fatty diacid

- Strong, reversible binding to albumin
- Slow receptor-mediated clearance

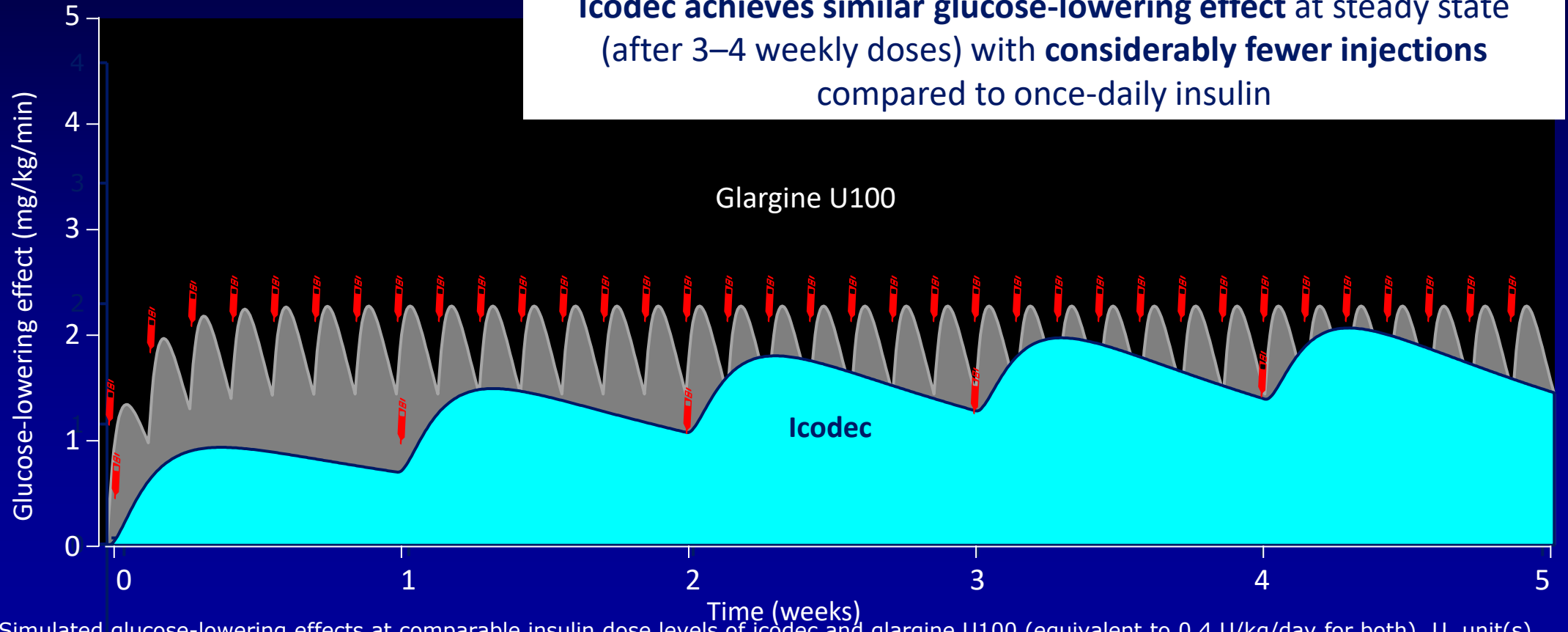
**2x (oligoethylene glycol(OEG) γ-L-Glu) spacer.*

1. Kjeldsen TB et al. 2021. J Med Chem.64(13):8942-8950; 2. Nishimura E et al. BMJ Open Diab Res Care 2021;9:e002301.

Pharmacodynamic modelling showed an increase in glucose-lowering effect over time

Based on phase 1 clinical data

Icodec achieves similar glucose-lowering effect at steady state (after 3–4 weekly doses) with **considerably fewer injections** compared to once-daily insulin



Simulated glucose-lowering effects at comparable insulin dose levels of icodec and glargine U100 (equivalent to 0.4 U/kg/day for both). U, unit(s).

1. Nishimura E. Expanding horizons of treating diabetes: Looking into newer possibilities. Lecture presented at 14th National Insulin Summit 2020; December 12, 2020. https://vimeo.com/489887511. Accessed 11 Jun 2021.

overview of the ONWARDS programme

Six phase 3 clinical trials

Insulin-naive T2D

ONWARDS 1

Physician survey · CGM

Insulin naïve T2D, N=970, 78 weeks

- Icodec + non-insulin anti-diabetic drugs
- Glargine U100 + non-insulin anti-diabetic drugs

Primary endpoint: HbA_{1c} non-inferiority
Secondary endpoints: TIR, HbA_{1c} superiority

ONWARDS 3

Insulin naïve T2D, N=580, 26 weeks

- Icodec + non-insulin anti-diabetic drugs
- IDeg+ non-insulin anti-diabetic drugs

Primary endpoint: HbA_{1c} non-inferiority

ONWARDS 5

Patient interview · PRO

RCT with real world elements
Insulin naïve T2D, N=1096, 52 weeks

- Icodec with DoseGuide
- OD basal insulin analogues

Primary endpoint: HbA_{1c} non-inferiority

Insulin-treated T2D

ONWARDS 2

PRO · CGM · Patient interview

Basal switch T2D, N=520, 26 weeks

- Icodec + non-insulin anti-diabetic drugs
- IDeg + non-insulin anti-diabetic drugs

Primary endpoint: HbA_{1c} non-inferiority

ONWARDS 4

CGM

Basal-bolus T2D, N=580, 26 weeks

- Icodec + IAsp ± non-insulin anti-diabetic drugs
- Glargine U100 + IAsp ± non-insulin anti-diabetic drugs

Primary endpoint: HbA_{1c} non-inferiority

Insulin-treated T1D

ONWARDS 6

PRO · CGM

Basal-bolus T1D, N=580, 52 weeks

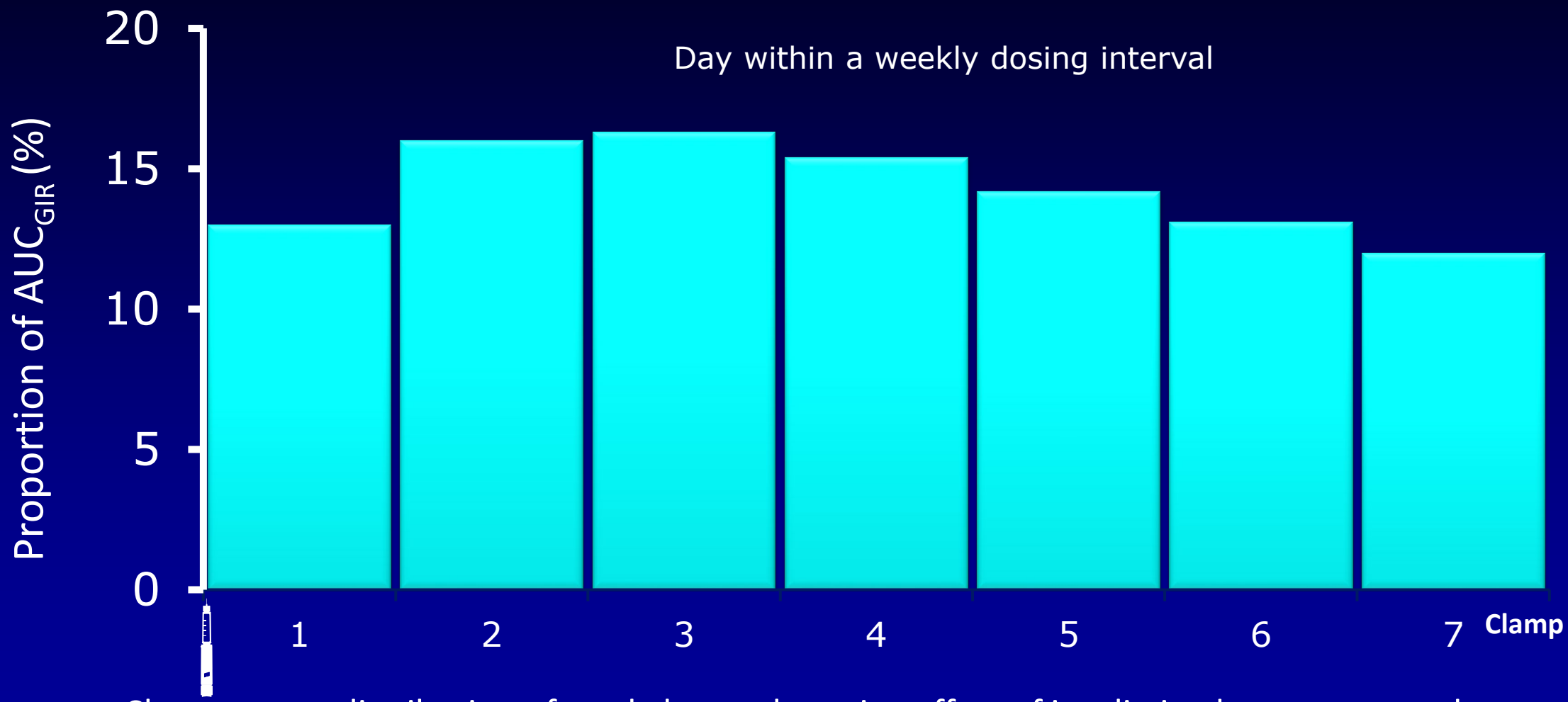
- Icodec + IAsp
- IDeg + IAsp

Primary endpoint: HbA_{1c} non-inferiority

HbA_{1c}, glycated haepe 1 diabetes; T2D, type 2 diabetes; TIR, time in range

Once-weekly basal insulin icodec: Looking ONWARDS from pharmacology to clinical trials Awadhesh Kumar Singh 2022 Sep;16(9):102615. doi: 10.1016/j.dsx.2022.102615, Rationale and design of the phase 3a development programme (ONWARDS 1-6 trials) investigating once-weekly i*moglobin; IAsp, insulin aspart; IDeg, insulin degludec; glargine U100, insulin glargine U100; n, number of subjects; OD, once daily; PRO, patient reported outcomes; RCT, randomised controlled trial; T1D, ty*nsulin icodec in diabetes Athena Philis-Tsimikas. . 2023 Feb;25(2):331-341. doi: 10.1111/dom.14871

modelled glucose-lowering effect of icodec



Close to even distribution of total glucose-lowering effect of insulin icodec over seven days

Modelled distribution of total glucose-lowering effect (AUC_{GIR}) of icodec within a dosing interval of one week at close to steady state. All three dose levels are combined. Individuals completing both glucose clamps and with pharmacokinetic data at steady state are included (n=32). Data are arithmetic mean.
AUC, area under the curve; GIR, glucose infusion rate; n, number of subjects.
1. Nishimura E et al. *BMJ Open Diab Res Care*. 2021;9(1).

Titration Algorithm for Basal Insulins

ONWARDS 1: Longest Trial of Once-Weekly Icodec vs Once-Daily Glargine U100 in Insulin Naïve T2DM

Pre-Breakfast SMBG		Glargine U100 Daily Dose Adjustments	Icodec Weekly Dose Adjustments
Up-Titrat	**Starting Doses:** Icodec 70 U and Glargine 10 U alues	+3 U	+20 U
Target	Mean of the SMBG values in the range 80–130 mg/dL	0 U	0 U
Down-Titration	Lowest SMBG value < 80 mg/dL	–3 U	–20 U

Dose adjustments done once a week based on three pre-breakfast SMBG values measured two days prior to titration and on the day of titration

N Engl J Med. 2023 Jul 27;389(4):297-308.

ONWARDS 1

Icodec in insulin-naïve T2D

984 individuals
- Insulin-naïve T2D treated with OADs* ± GLP-1RA s.c.
- Age ≥18 years
- HbA_{1c}: 7.0–11.0%

Once-weekly icodec ± non-insulin glucose-lowering medications

Once-daily glargine U100 ± non-insulin glucose-lowering medications

Trial information
Randomised open-label
Treat-to-target
Double-blinded CGM (Dexcom G6®) at specific time periods

Trial objective
- To investigate the effect on glycaemic control and safety of once-weekly insulin icodec in comparison with once-daily insulin glargine U100, both in combination with non-insulin glucose-lowering agents, in insulin-naïve T2D

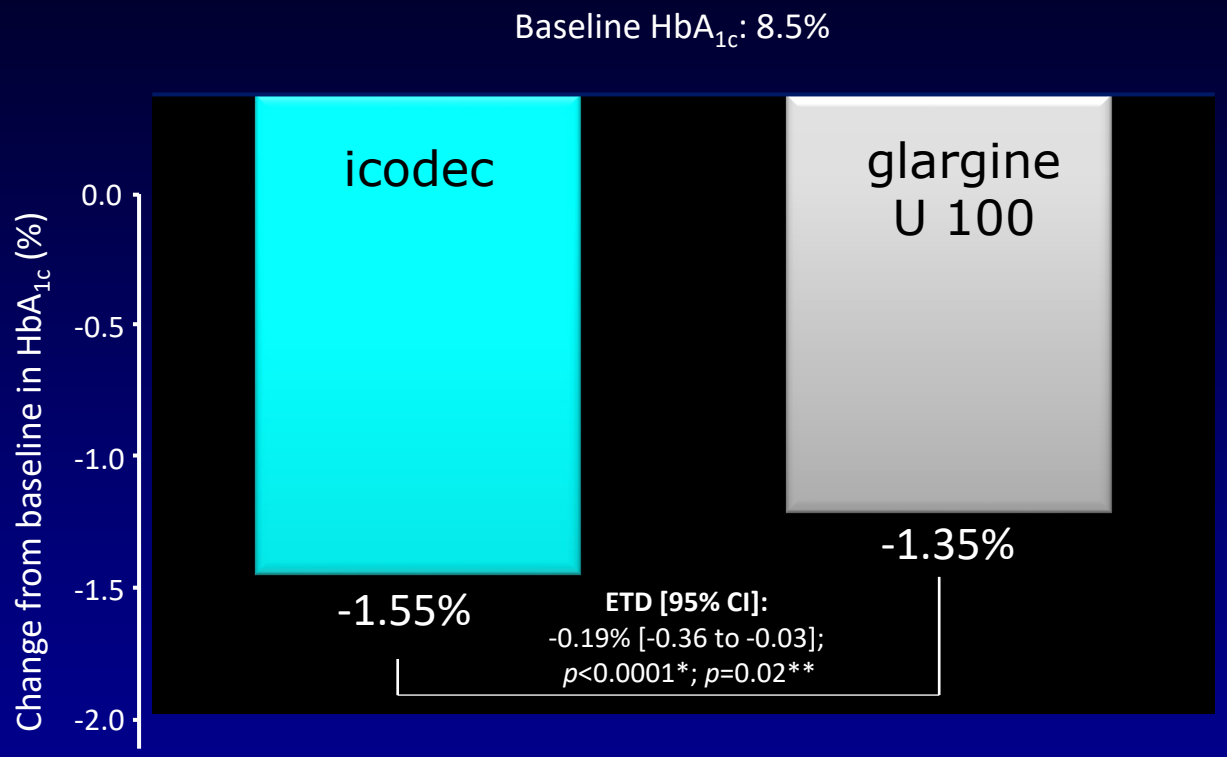
Primary endpoint
- Change in HbA_{1c}

Secondary supportive endpoints
- Changes in FPG, TIR, TAR, TBR, body weight
- Weekly insulin dose
- Clinically significant or severe hypoglycaemia†

*Pre-trial all OADs including oral GLP-1RAs are allowed but sulphonylureas and glinides are to be discontinued at randomisation. †Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
ClinicalTrials.gov Identifier: NCT04460885. CGM, continuous glucose monitoring; FPG, fasting plasma glucose; GLP-1RA, glucagon like peptide–1 receptor agonist; OADs, oral glucose-lowering medications;; s.c., subcutaneous; TAR, time-above range; TBR, time-below range; TIR, time-in range.
1. Philis-Tsimikas A et al. *Diabetes Obes Metab*. 2022;25(2):331-341; 2. Rosenstock J, et al. *N Engl J Med* 2023;10.1056/NEJMoa2303208.

ONWARDS 1 : change in HbA_{1c} and safety summary

Icodec in insulin-naïve T2D - *main phase (Baseline to week 52)*



Rate of severe or clinically significant hypoglycaemia† (events per patient-year exposed to treatment)

Icodec	0.30
Glargine U100	0.16

No statistical difference in estimated rates of clinically significant or severe hypoglycaemia[b]

The trial demonstrated non-inferiority and superiority in HbA_{1c} change from baseline to week 52 with insulin icodec compared to insulin glargine U100[a]

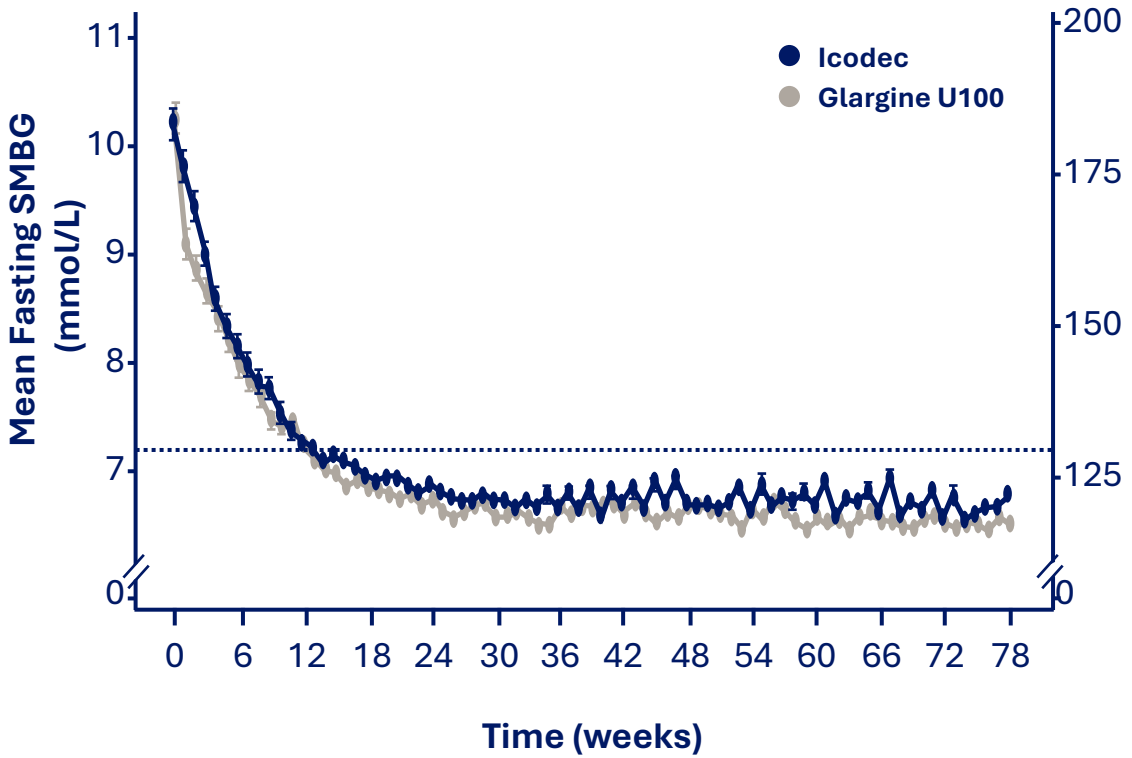
† Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.

*p-value for the test of noninferiority of icodec vs glargine U100 (noninferiority confirmed); **p-value for the test of superiority of icodec vs glargine U100 (superiority confirmed). In-trial. Full analysis set. Observed data are shown as mean (symbol) ± standard error of the mean (error bars). ETD, estimated treatment difference. [a]Analysis of covariance with treatment and region as fixed effects, and the baseline value of the response as a covariate. [b]Negative binomial regression model with log-link function and the logarithm of the period in which episodes will be considered treatment emergent as offset; fixed factors include treatment and region.

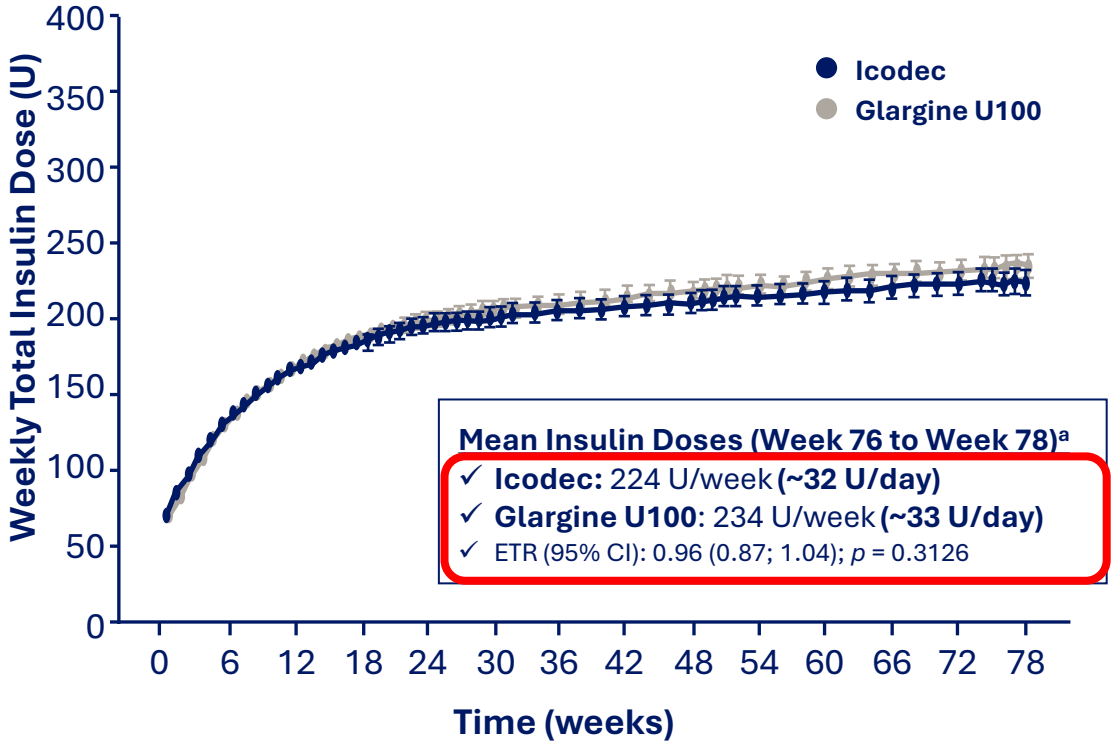
1. Rosenstock J, et al. *N Engl J Med* 2023;10.1056/NEJMoa2303208.

ONWARDS 1: Longest Trial of Once-Weekly Icodec vs Once-Daily Glargine U100 in Insulin Naïve T2DM

Fasting Glucose Over Time from SMPG for Dose Adjustments



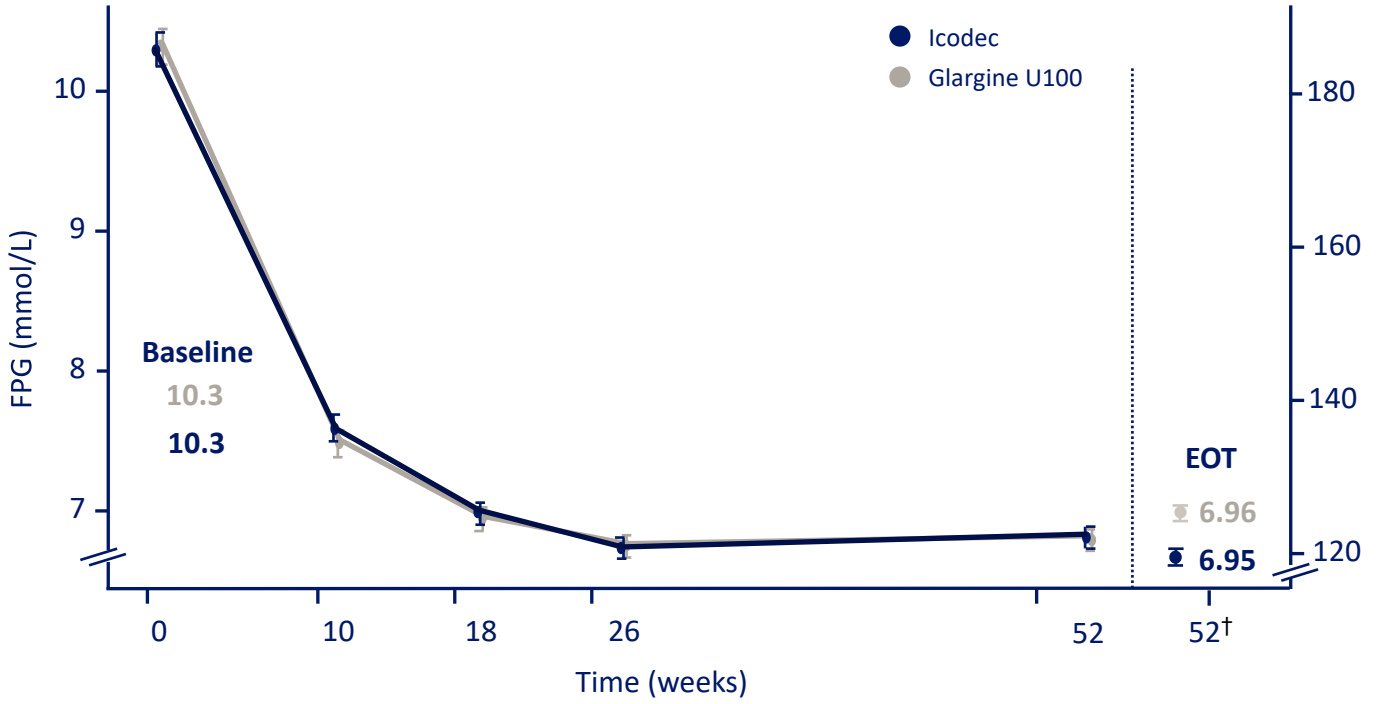
Weekly Total Insulin Doses Over Time

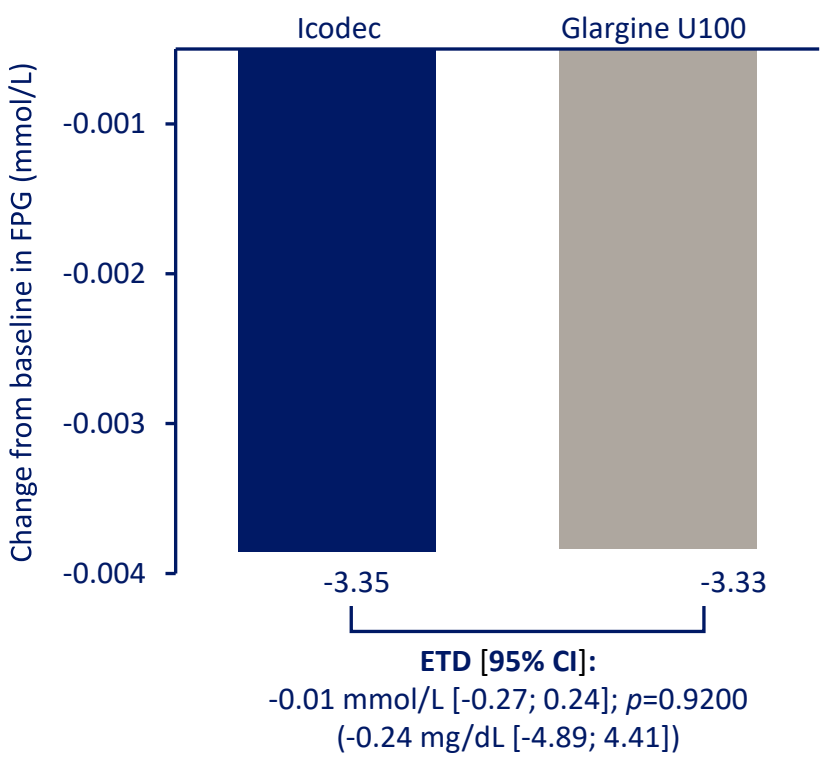


N Engl J Med. 2023 Jul 27;389(4):297-308.

ONWARDS 1: Fasting plasma glucose over time and at week 52

Icodec in insulin-naïve T2D





No statistically significant difference between groups in **change in FPG** from baseline to week 52

Estimated mean FPG at week 52 and week 78 based on ANCOVA with data derived from multiple imputation, with treatment and region as fixed effects, and the baseline value of the response as a covariate. In-trial. Full analysis set. Observed data including data obtained after premature treatment discontinuation. Observed data are shown as mean (symbol) ± standard error of the mean (error bars)

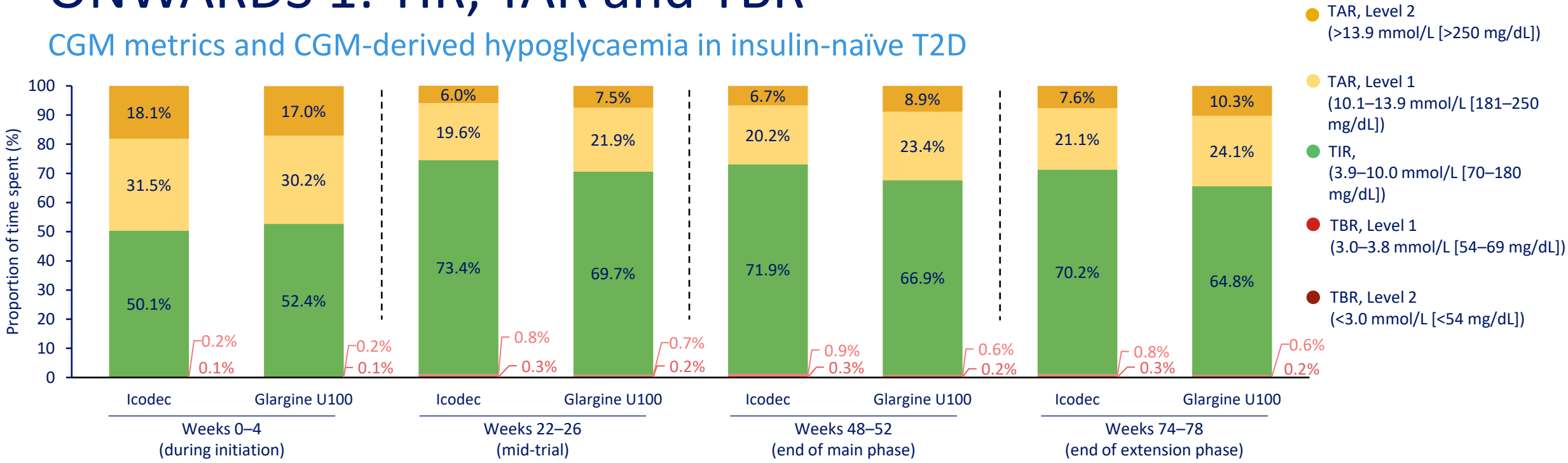
CI, confidence interval; ETD, estimated treatment difference; FPG, fasting plasma glucose.

1. Rosenstock J, et al. *N Engl J Med* 2023;10.1056/NEJMoa2303208; 2. Rosenstock J et al. 2023 ADA Scientific Sessions. 179-OR.

Objective: To investigate the efficacy and safety of once-weekly icodec versus once-daily glargine U100 in insulin-naïve individuals with T2D using CGM-based metrics and **CGM-derived hypoglycaemia** duration via ***post hoc*** **analyses from ONWARDS 1**

ONWARDS 1: TIR, TAR and TBR

CGM metrics and CGM-derived hypoglycaemia in insulin-naïve T2D

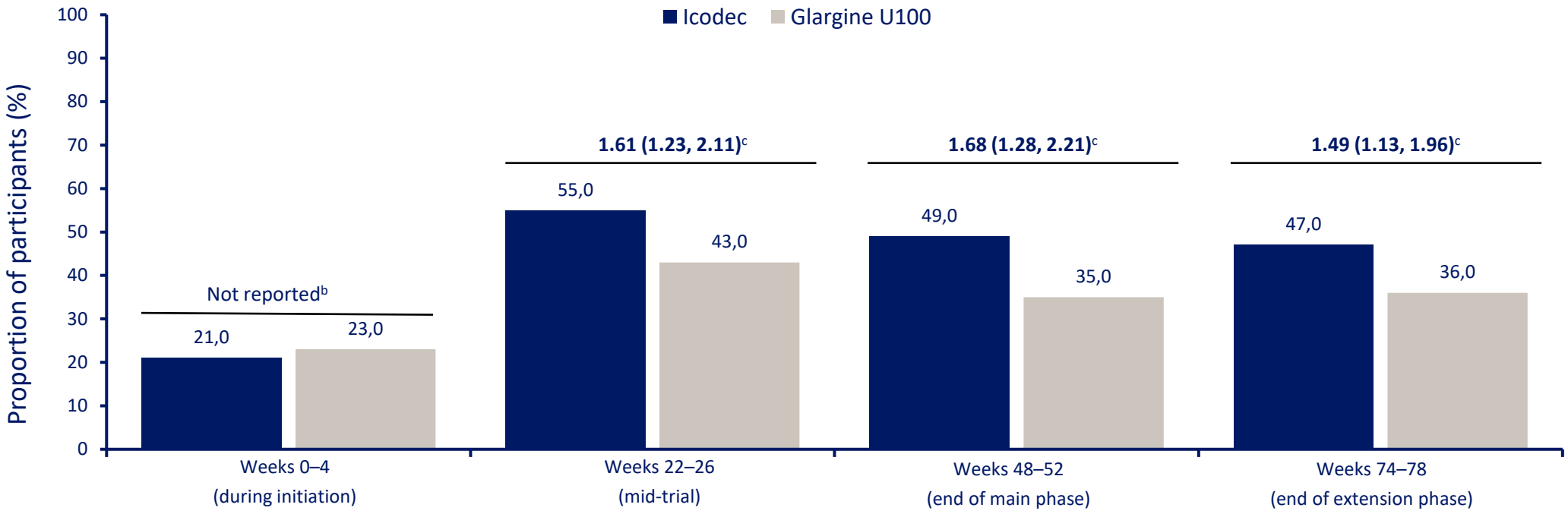


		Weeks 0–4 (during initiation)	Weeks 22–26 (mid-trial)	Weeks 48–52 (end of main phase)	Weeks 74–78 (end of extension phase)
Estimated treatment difference (95% confidence interval)	$TAR_{>10.0\ mmol/L}$	2.34 (−1.09, 5.77)[d]	**−3.69 (−6.03, −1.34)**[d]	**−4.58 (−6.99, −2.17)**[d]	**−4.65 (−7.20, −2.10)**[d]
	$TIR_{3.9–10.0\ mmol/L}$	−2.39 (−5.79, 1.02)[d]	**3.57 (1.27, 5.87)**[d]	**4.27 (1.92, 6.62)**[d,e]	**4.41 (1.92, 6.90)**[d]
Estimated treatment ratio (95% confidence interval)	$TBR_{<3.9\ mmol/L}$	1.20 (0.85, 1.70)[f]	1.10 (0.89, 1.38)[f]	**1.48 (1.19, 1.84)**[f]	**1.34 (1.07, 1.68)**[f]
	$TBR_{<3.0\ mmol/L}$	1.27 (0.81, 1.97)[f]	1.16 (0.86, 1.55)[f]	1.27 (0.94, 1.71)[f]	1.20 (0.89, 1.61)[f]

Data based on the full analysis set. Bold text indicates a statistically significant difference in favour of icodec (TIR and TAR) or glargine U100 (TBR <3.9 mmol/L [70 mg/dL]). Estimated treatment difference = icodec – glargine U100; estimated treatment ratio = icodec/glargine U100.
[d]Analysis of variance model, with region and randomised treatment as fixed factors. [e]Confirmatory endpoint. [f]Negative binomial model using the number of recorded measurements below range, with a log-link function and the logarithm of the total number of recorded measurements as an offset. Region and randomized treatment were included as fixed factors. CGM, continuous glucose monitoring; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range. 1. Battelino T et al. *Lancet Diabetes Endocrinol* 2023;11:42–57; 2. Battelino T et al. *Diabetes Care* 2019; 42:1593–603; 3. Bergenstal R. et al. 2023 ADA scientific sessions. ePoster 85-LB

ONWARDS 1: achievement of combined triple CGM target[a]

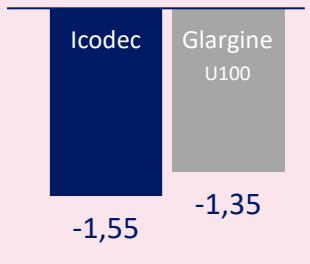
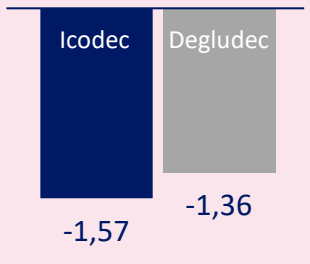
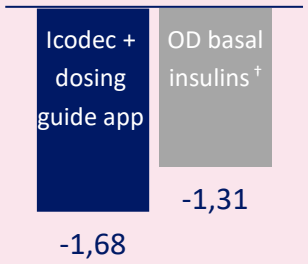
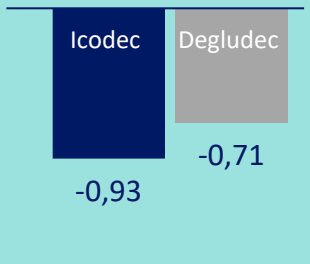
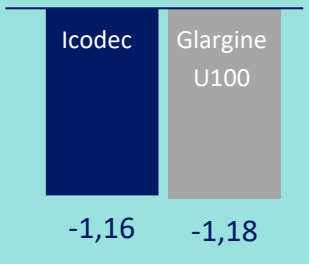
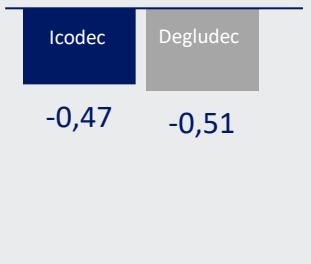
CGM metrics and CGM-derived hypoglycaemia in insulin-naïve T2D



More participants achieved the triple composite endpoint of TIR >70%, TAR <25% and TBR (<3.9 mmol/L [70 mg/dL]) < 4% at weeks 22–26, 48–52 and 74–78 with icodec versus glargine U100

Data based on full analysis set. Bold text indicates a statistically significant difference in favour of icodec. Data outside the bars are odds ratios (95% confidence intervals).
[a]CGM targets: TIR (3.9-10.0 mmol/L [70-180 mg/dL]) > 70%, TAR (>10.0 mmol/L [180 mg/dL]) < 25% and TBR (<3.9 mmol/L [70 mg/dL]) < 4%. [b]Odds ratio (icodec/glargine U100) for weeks 0–4 was not calculated because it was not at steady state. [c]The binary response was analysed using a binary logistic regression model (logit link) with treatment and region as fixed factors
CGM, continuous glucose monitoring; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range.
1. Bergenstal R. et al. 2023 ADA scientific sessions. ePoster 85-LB.

ONWARDS programme: primary endpoint

	ONWARDS 1 BASAL INITIATION	***ONWARDS 3*** BASAL INITIATION	***ONWARDS 5*** BASAL INITIATION	***ONWARDS 2*** BASAL SWITCH	***ONWARDS 4*** BASAL/BOLUS SWITCH	***ONWARDS 6*** BASAL/BOLUS SWITCH
Baseline HbA_{1c}	8.5	8.5	8.9	8.13	8.3	7.61
Estimated change in HbA_{1c} (%) from baseline						
Endpoint assessed (week)	52	26	52	26	26	26
	ETD [95% CI]: -0.19% [-0.36 to -0.03]; *p*<0.0001*; *p*=0.02**	**ETD [95% CI]:** -0.21% [-0.34 to -0.08]; *p*<0.001*; *p*=0.002**	**ETD [95% CI]:** -0.38% [-0.66 to -0.09]; *p*<0.0001*, *p*=0.009**	**ETD [95% CI]:** -0.22% [-0.37 to -0.08]; *p*<0.0001*; *p*=0.0028**	**ETD [95% CI]:** 0.02% [-0.11 to 0.15]; *p*<0.0001*	**ETD [95% CI]:** 0.05% [-0.13 to 0.23] *p*=0.0065*

*p-value for the test of noninferiority of icodec vs comparator (noninferiority confirmed); **p-value for the test of superiority of icodec vs comparator (superiority confirmed). †insulin degludec or insulin glargine U100/U300; HbA_{1c}, glycated haemoglobin; CI, confidence interval; ETD, estimated treatment difference; OD, once-daily.

1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116; 2. Lingvay I et al. *JAMA*. 2023:10.1001/jama.2023.11313; 3. Lingvay I et al. 2023 ADA Scientific Sessions. 178-OR; 4. Bajaj H. 2023 ADA Scientific Sessions. 803-P. 5. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425. 6. Mathieu C et al. *Lancet*. 2023;401(10392):1929-40; 7. Russell-Jones D et al. *Lancet*. 2023: DOI: 10.1016/S0140-6736(23)02179-7.

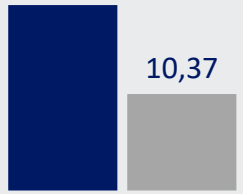
ONWARDS programme: secondary endpoints

	***ONWARDS* 1** **BASAL INITIATION**		***ONWARDS* 3** **BASAL INITIATION**		***ONWARDS* 5** **BASAL INITIATION**		***ONWARDS* 2** **BASAL SWITCH**		***ONWARDS* 4** **BASAL/BOLUS SWITCH**		***ONWARDS* 6** **BASAL/BOLUS SWITCH**	
	Icodec	Glargine U100	Icodec	Degludec	Icodec + dosing guide app	OD basal insulins[†]	Icodec	Degludec	Icodec	Glargine U100	Icodec	Degludec
Attainment of HbA_{1c} <7.0% (<53 mmol/mol)	57.6%	45.4%	56.8%	41.6%	46.8%	34.7%	40.3%	26.5%	40.7%	45.5%	40.2%	45.7%
Attainment of HbA_{1c} <7.0% (<53 mmol/mol) assessed (week)	52		26		52		26		26		26	
Proportion of time spent in target* range (3.9–10·0 mmol/L[70–180 mg/dL])	71.9%	66.9%	-	-	-	-	63.1%	59.5%	66.9 %	66.4%	59.1%	60.8%
Bodyweight change from baseline, kg	+2.3	+1.8	+2.8	+2.3	+2.3	+1.5	+1.40	-0.3	+2.7	+2.2	+1.29	+1.01
Weekly basal insulin dosage, U/week**	214	222	204	187	227	185	268	244	305	279	170	151

[†]insulin degludec or insulin glargine U100/U300; *assessed during the last 4 weeks of treatment, main phase. **assessed during the last 2 weeks of treatment. OD, once-daily.

1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116; 2. Lingvay I et al. *JAMA*. 2023:10.1001/jama.2023.11313; 3. Bajaj H. 2023 ADA Scientific Sessions. 803-P. 4. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol.* 2023;11(6):414-425. 5. Philis-Tsimikas A et al. 2022. EASD Annual Meeting. S42.; 6. Mathieu C et al. *Lancet*. 2023;401(10392):1929-40; 7. Mathieu C et al. 2022. DTS 22nd Annual Meeting. Virtual. 2 Nov 2022; 7. Russell-Jones D et al. *Lancet*. 2023: DOI: 10.1016/S0140-6736(23)02179-7.

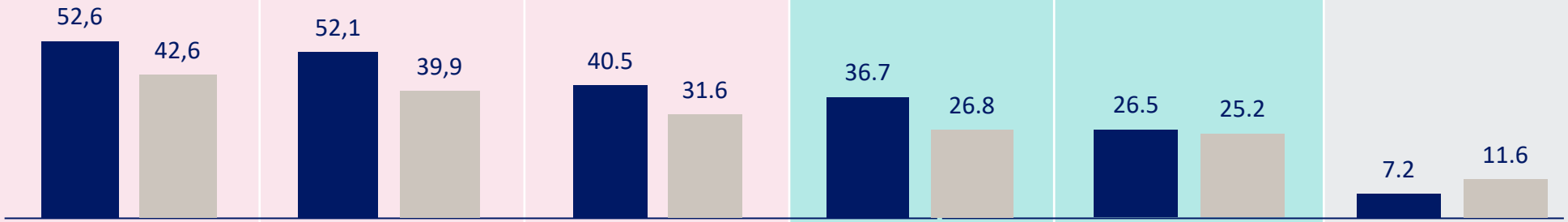
ONWARDS trials: hypoglycaemia

	ONWARDS 1 BASAL INITIATION	***ONWARDS 3*** BASAL INITIATION	***ONWARDS 5*** BASAL INITIATION	***ONWARDS 2*** BASAL SWITCH	***ONWARDS 4*** BASAL/BOLUS SWITCH	***ONWARDS 6*** BASAL/BOLUS SWITCH
Estimated rate of clinically significant or severe hypoglycaemia* (events per PYE)						
	Icodec vs Glargine U100	Icodec vs Degludec	Icodec + dosing guide app vs OD basal insulins†	Icodec vs Degludec	Icodec vs Glargine U100	Icodec vs Degludec
Endpoint assessed (week)	0–52	0–31	0–57	0–31	0–31	0–26
	ERR [95% CI]: 1.64 [0.98 to 2.75]; *p*=0.06	**ERR [95% CI]:** 1.82 [0.87 to 3.80]; *p*=0.11	**ERR [95% CI]:** 1.17 [0.73 to 1.86]; *p*=0.52	**ERR [95% CI]:** 1.93 [0.93 to 4.02]; *p*=0.078	**ERR [95% CI]:** 0.99 [0.73 to 1.33]; *p*=0.93	**ERR [95% CI]:** 1.89 [1.54 to 2.33]; *p*<0.0001

*Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. † insulin degludec or insulin glargine U100/U300; CI, confidence interval; ERR, estimated rate ratio; OD, once-daily; PYE, patient years of exposure.

1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116; 2. Lingvay I et al. *JAMA*. 2023:10.1001/jama.2023.11313; 3. Bajaj H. 2023 ADA Scientific Sessions. 803-P. 4. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425. 5. Mathieu C et al. *Lancet.* 2023;401(10392):1929-40; 6. Rosenstock J et al. 2023 ADA Scientific Sessions. 179-OR; 7. Lingvay I et al. 2023 ADA Scientific Sessions. 178-OR; 8. Russell-Jones D et al. *Lancet*. 2023: DOI: 10.1016/S0140-6736(23)02179-7.

ONWARDS trials: composite endpoint

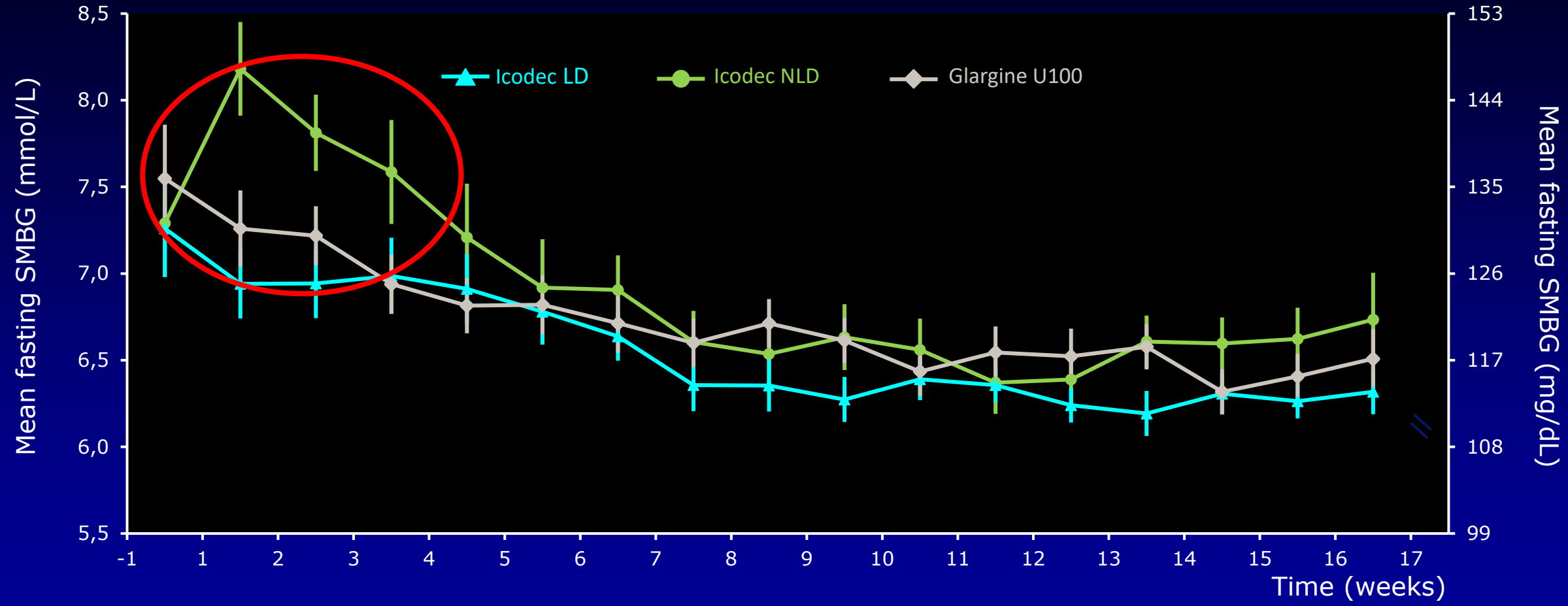
	ONWARDS 1 BASAL INITIATION	***ONWARDS 3*** BASAL INITIATION	***ONWARDS 5*** BASAL INITIATION	***ONWARDS 2*** BASAL SWITCH	***ONWARDS 4*** BASAL/BOLUS SWITCH	***ONWARDS 6*** BASAL/BOLUS SWITCH
Attainment of HbA_{1c} <7.0% (<53 mmol/mol) without clinically significant or severe hypoglycaemia						
Endpoint assessed (week)	52	26	52	26	26	52
	EOR [95% CI]: 1.5 [1.15 to 1.94] *p*=0.0028*	**EOR [95% CI]:** 1.64 [1.16, 2.33] *p*=0.0054*	**EOR [95% CI]:** 1.47 [1.13, 1.92] *p*=0.004*	**EOR [95% CI]:** 1.59 [1.07 to 2.36] *p*=0.0223*	**EOR [95% CI]:** 1.1 [0.7 to 1.6] *p*=0.735	**EOR [95% CI]:** 0.59 [0.37 to 0.95] *p*=0.031*

Clinically significant hypoglycaemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. † insulin degludec or insulin glargine U100/U300; CI, confidence interval; EOR, estimated odds ratio; OD, once-daily; PYE, patient years of exposure; *p-value indicating statistical significance.

1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116; 2. Lingvay I et al. *JAMA*. 2023:10.1001/jama.2023.11313; 3. Bajaj H. 2023 ADA Scientific Sessions. 803-P. 4. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425. 5. Mathieu C et al. *Lancet.* 2023;401(10392):1929-40; 6. Rosenstock J et al. 2023 ADA Scientific Sessions. 179-OR; 7. Lingvay I et al. 2023 ADA Scientific Sessions. 178-OR; 8. Mathieu C et al. 2022. DTS 22nd Annual Meeting. Virtual. 2 Nov 2022; 9. Philis-Tsimikas A et al. 2022. EASD Annual Meeting. S42; 10. Russell-Jones D et al. *Lancet*. 2023: DOI: 10.1016/S0140-6736(23)02179-7.

Fasting SMBG for dose adjustment over time

Switching from OD/BID basal insulin to OW icodec



Mean fasting SMBG decreased in the icodec LD and glargine U100 groups over the course of the study. In the icodec NLD group, there was a transient increase in fasting SMBG, before lowering to a level similar to that in other treatment groups around week 5

Full analysis set. Data are mean ± SEM. Trial product estimand. Fasting SMBG was measured for dose adjustment and was not as a pre-specified endpoint.
BID, twice-daily; LD, loading dose; NLD, no loading dose; OD, once-daily; OW, once-weekly; SEM, standard error of the mean; SMBG, self-measured blood glucose.

1. 1. Bajaj H et al. *Diabetes Care*. 2021; 44(7):1586–1594.

popolazioni speciali

- **Anziani**
  - **Non** è richiesto alcun aggiustamento della dose per i pazienti anziani.
- **Compromissione renale** (1)
  - **Non** è richiesto alcun aggiustamento della dose nei pazienti con compromissione renale. Nei pazienti con compromissione renale, si raccomanda un monitoraggio glicemico più frequente
- **Compromissione epatica** (2)
  - **Non** è richiesto alcun aggiustamento della dose per i pazienti con compromissione della funzionalità epatica. Nei pazienti con compromissione epatica, si raccomanda un monitoraggio glicemico più frequente.

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

2. 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

Dose dimenticata

Se una dose viene saltata, si raccomanda di somministrarla il prima possibile.

- Se sono trascorsi **meno di 3 giorni** alla dose dimenticata, i pazienti con diabete di tipo 2 possono riprendere il programma di dosaggio originale una volta a settimana. Deve essere effettuato il monitoraggio della glicemia a digiuno.

- Se sono trascorsi **più di 3 giorni**, la dose dimenticata deve essere comunque somministrata il prima possibile. Lo schema di dosaggio una volta alla settimana verrà quindi modificato per ripartire dal giorno della settimana in cui è stata somministrata la dose dimenticata.

- Se si vuole mantenere il **giorno originale** della somministrazione una volta alla settimana, l'intervallo di tempo tra le dosi successive può essere successivamente prolungato fino ad ottenere infine lo stesso giorno di somministrazione.

Insulina settimanale: quando e a chi?

Diabetici di tipo 2 già in trattamento con almeno 2-3 farmaci (met, SGLT-2i, GLP-1 RA, Pio) con ancora un controllo glicemico inadeguato.

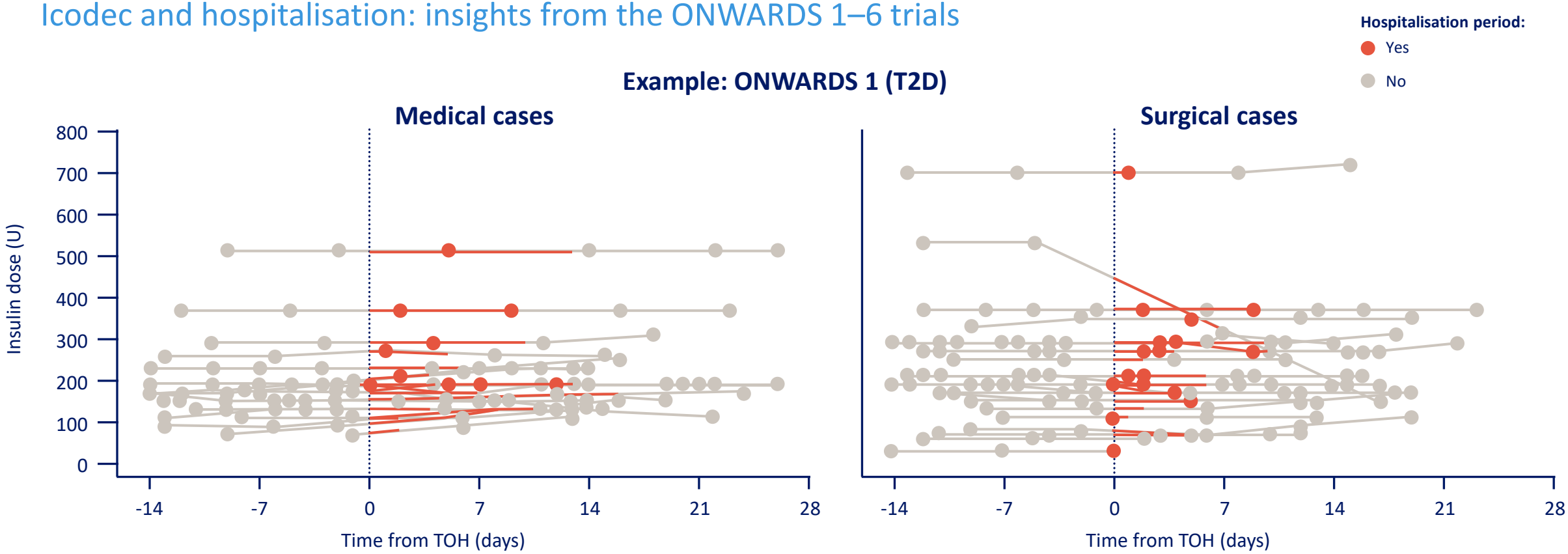
Diabetici di tipo 2 già in trattamento con insulina basale in difficoltà con la terapia quotidiana.

Diabetici anziani, fragili che necessitano del caregiver per la terapia insulinica (in questo caso il target glicemico va individualizzato)

R.Trevisan et al., Diabetologia 2024

Icodec dose during and around hospitalisation

Icodec and hospitalisation: insights from the ONWARDS 1–6 trials



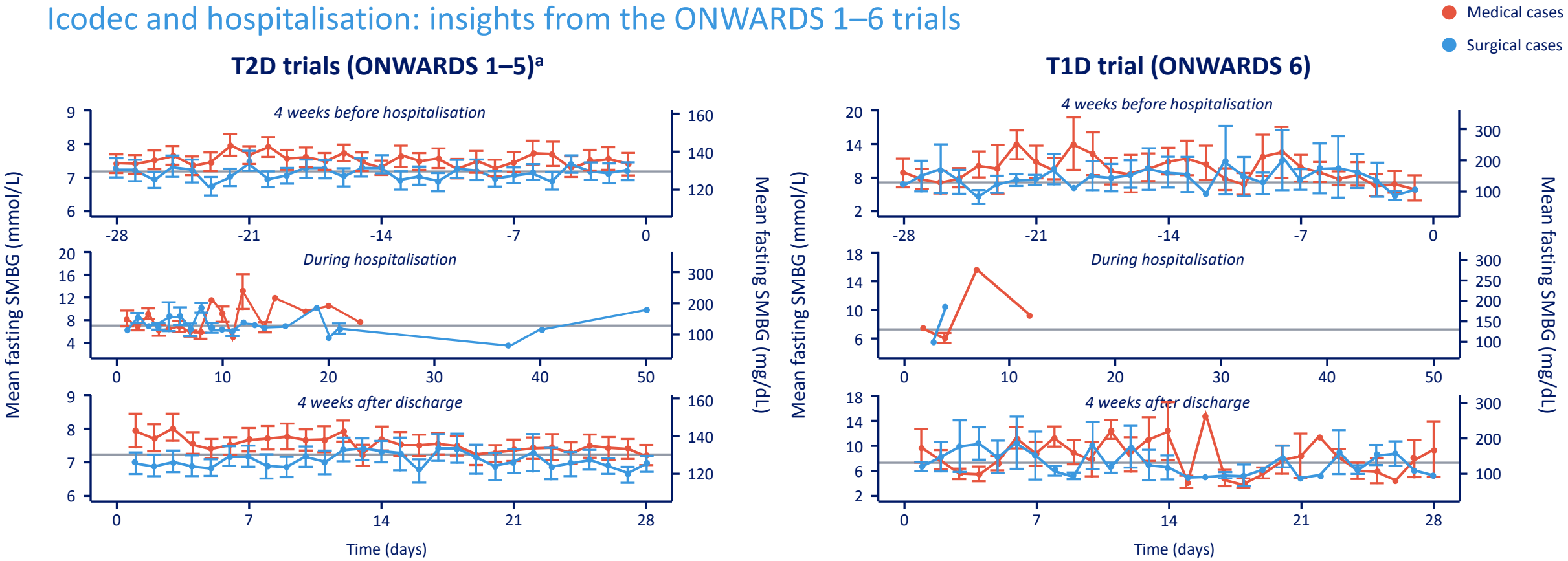
Overall, for participants receiving icodec, the **dose remained fairly stable and uninterrupted during hospitalisation**

Filled circles represent administration of an icodec dose. Doses from 14 days before TOH to 14 days after TOD are shown. Red lines represent the hospitalisation period. Grey lines represent the pre- and post-hospitalisation periods. The end of the red segment of each line indicates TOD.
TOD, time of discharge; TOH, time of hospitalisation; U, units.

1. Philis-Tsimikas A et al. EASD 2023 Annual Meeting. SO-781.

Glycaemic control: SMBG levels

Icodec and hospitalisation: insights from the ONWARDS 1–6 trials



Few SMBG measurements were recorded during hospitalisation; based on available data, no major impact on glycaemic control was observed

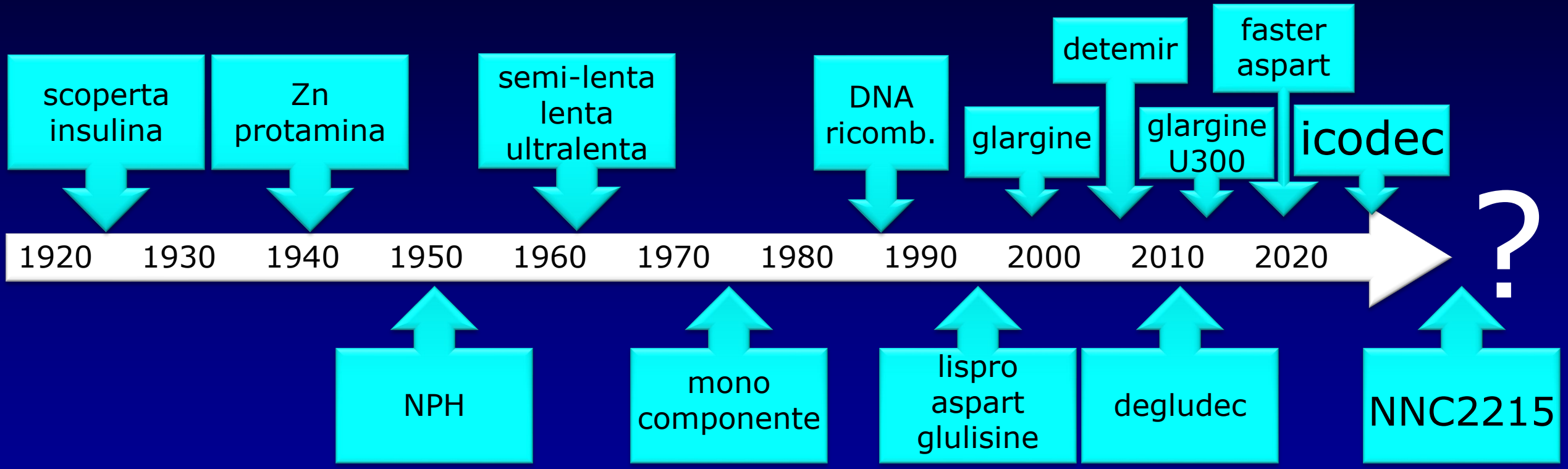
Observed data shown as mean ± SEM. Horizontal grey lines at 7.2 mmol/L represent the pre-breakfast SMBG value above which an increase in treatment dose is required. SMBG assessed with a glucose meter as plasma equivalent values of capillary whole blood glucose.

[a]Graphs present pooled data from ONWARDS 1–5.

SEM, standard error of the mean; SMBG, self-measured blood glucose.

1. Philis-Tsimikas A et al. EASD 2023 Annual Meeting. SO-781.

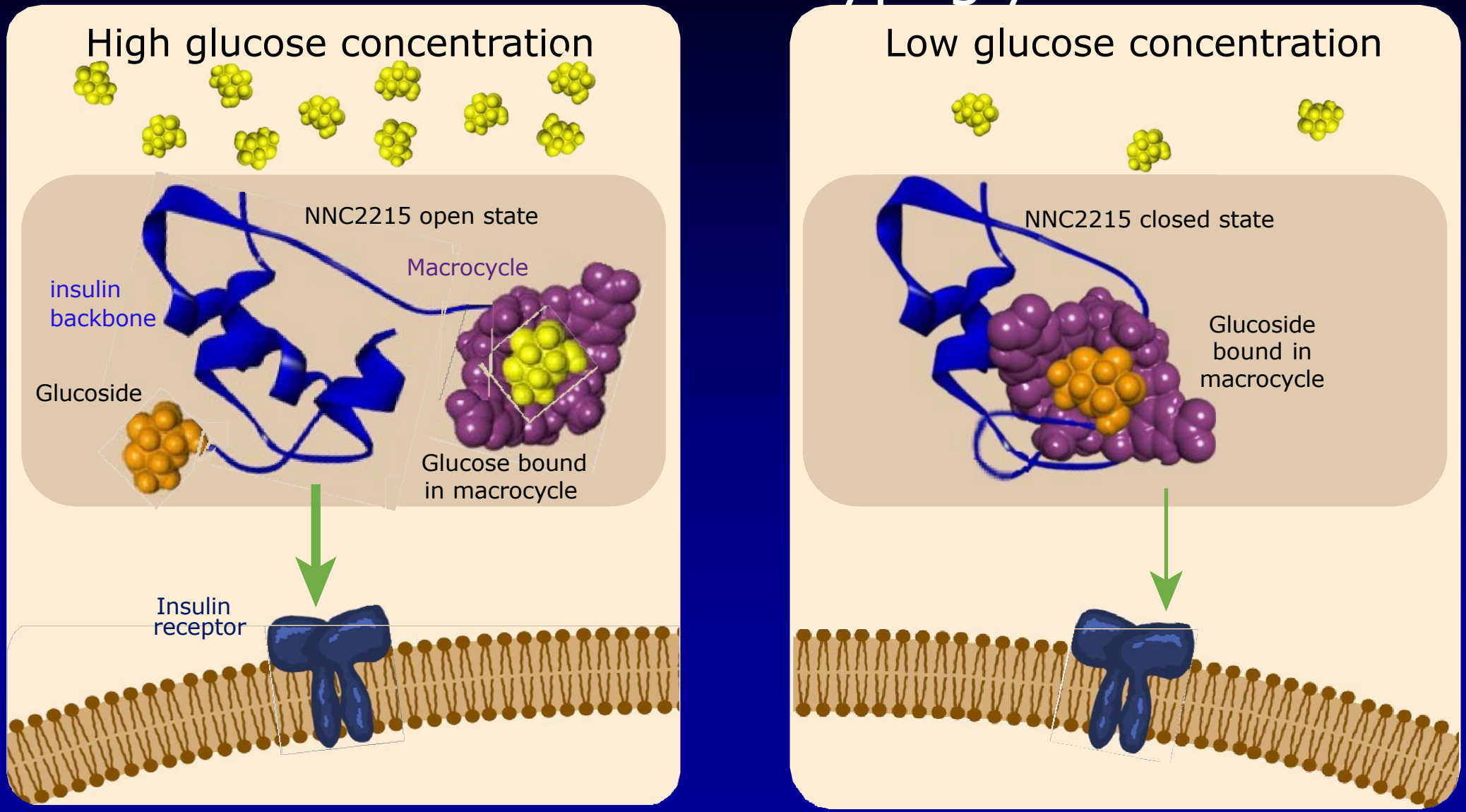
un secolo di insulina



NPH, neutral protamine Hagedorn

Adapted from Cahn *et al. Lancet Diabetes Endocrinol* 2015;3:638–52; Kim & Plosker. *Drugs* 2015;75:1679–86

NNC2215: Glucose-sensitive insulin
with attenuation of hypoglycaemia



Hoeg-Jensen T et al.: Nature 634:944, 2024 doi: 10.1038/s41586-024-08042-3. Epub 2024 Oct 16

Conclusioni

I dati disponibili sono incoraggianti sia in termini di efficacia nel controllo glicemico che sul basso rischio di ipoglicemia.

A 100 anni dalla scoperta dell'insulina, la possibilità di ridurre drasticamente il numero di iniezioni offre la grande opportunità di semplificare (e anche di migliorare) la terapia insulinica nei diabetici di tipo 2.

ora sta a noi