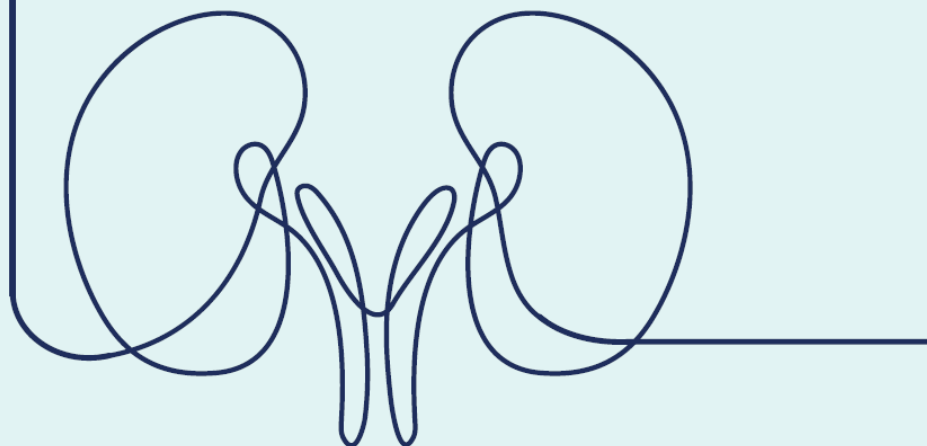




Insulina settimanale nel diabete tipo 2: come e quanto funziona

Andrea Giaccari

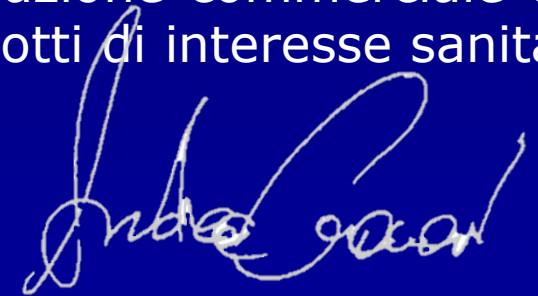


DICHIARAZIONE CONFLITTO D'INTERESSE DOCENTI

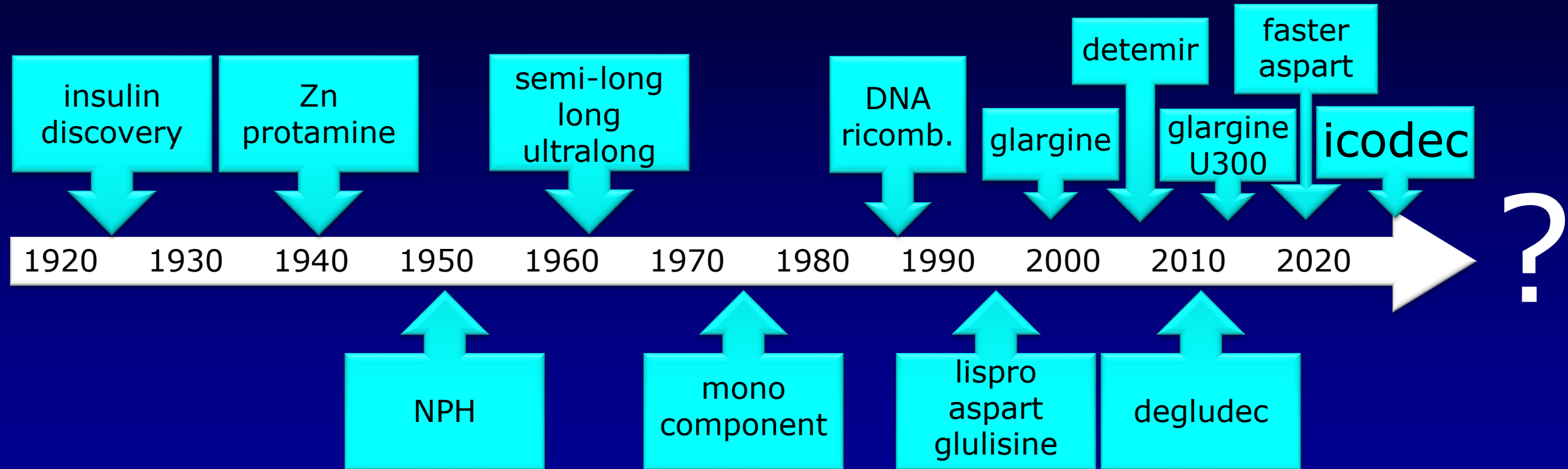
Il sottoscritto prof. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abbott
- 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.).

A handwritten signature in white ink, appearing to read 'Andrea Giaccari', is located in the bottom right corner of the slide.

a century of insulin



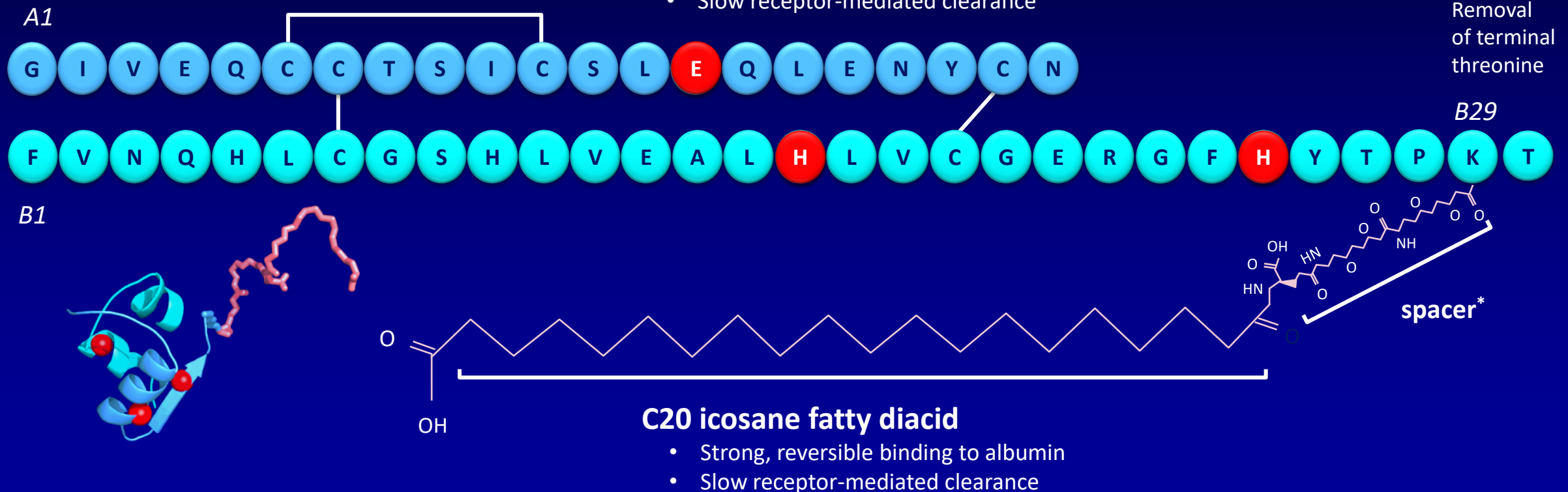
NPH, neutral protamine Hagedorn

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

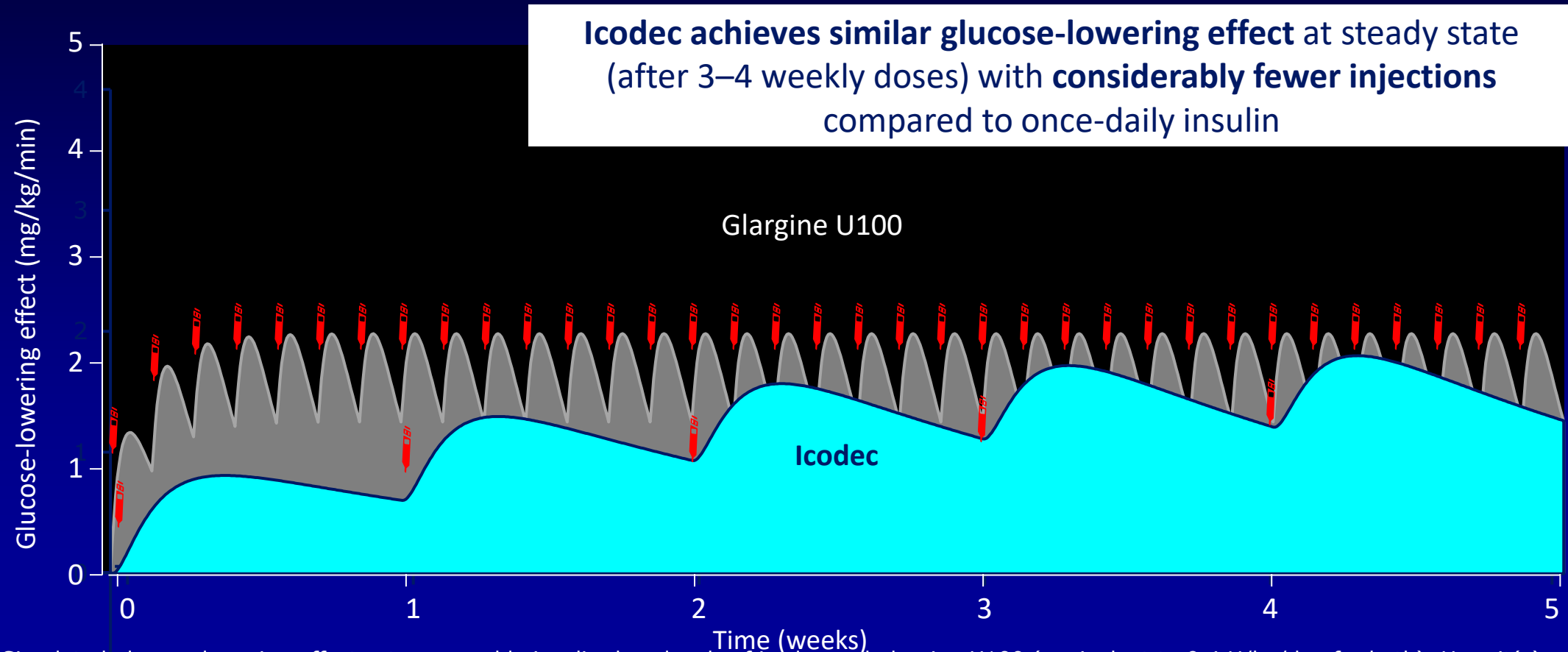


*2x (oligoethylene glycol(OEG) γ -L-Glu) spacer.

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

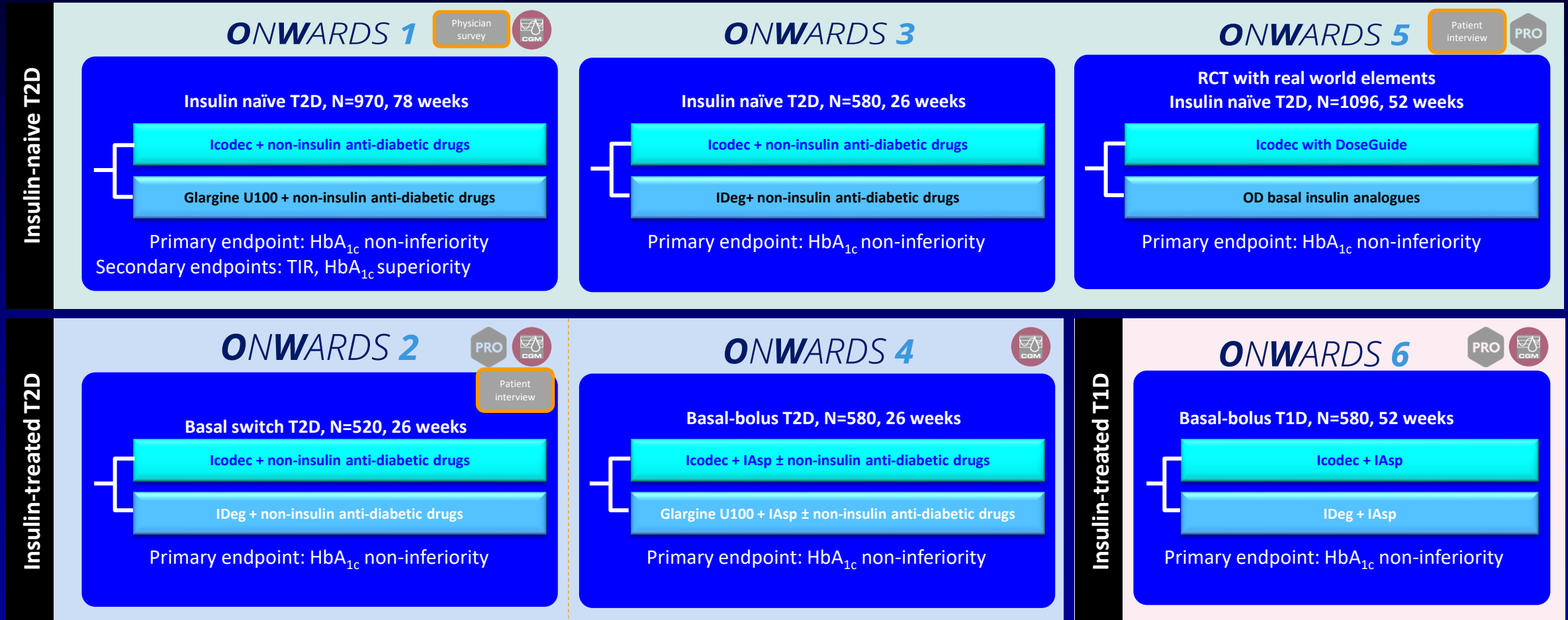
Based on phase 1 clinical data



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



HbA_{1c}, glycated haemoglobin; 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 imoglibin; 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, type 1 diabetes; Icodec, insulin icodec in diabetes Athena Philis-Tsimikas. 2023 Feb;25(2):331-341. doi: 10.1111/dom.14871

Titration Algorithm for Basal Insulins

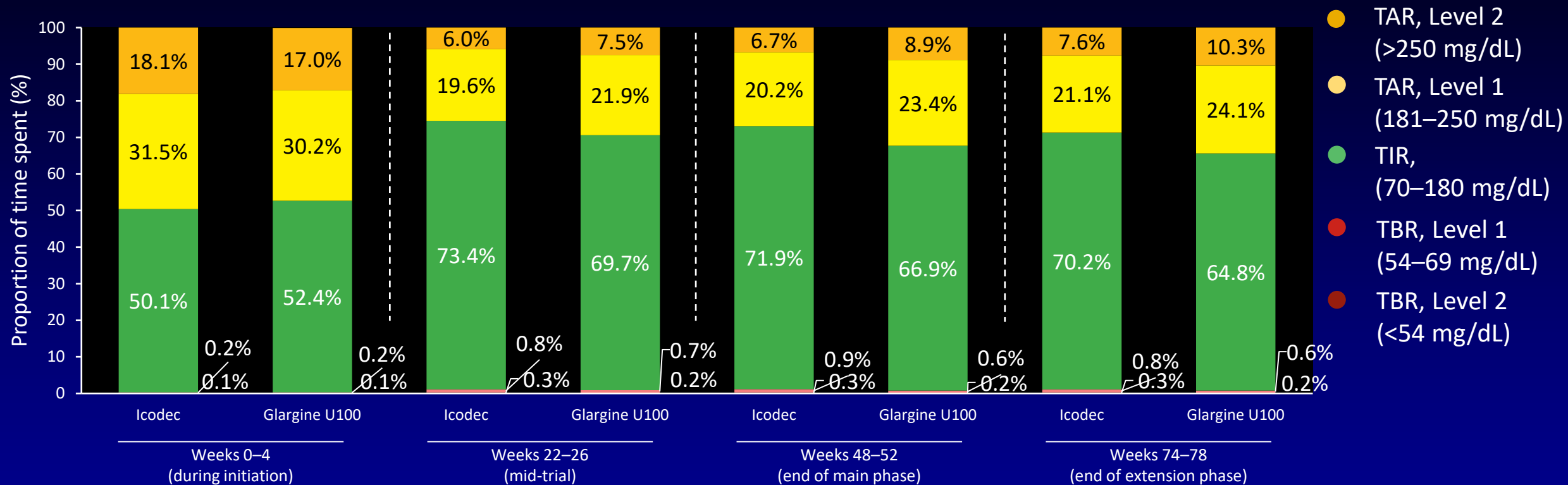
ONWARDS 1: Longest Trial of Once-Weekly Icodec vs Once-Daily Glargine U100 in Insulin Naïve T2DM

Pre-Breakfast SMBG		Glargine U100 Daily Dose Adjustments	Icodec Weekly Dose Adjustments
Up-Titration	Starting Doses: Icodec 70 U and Glargine 10 U	+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

ONWARDS 1: TIR, TAR and TBR

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



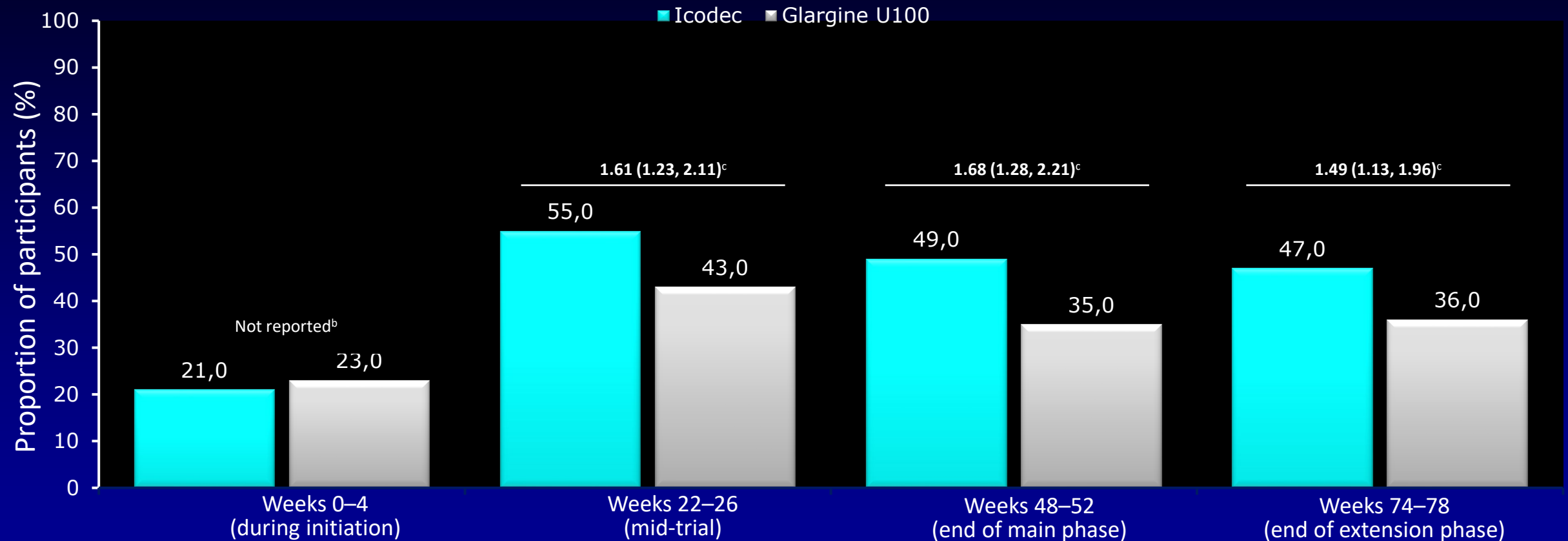
		Weeks 0–4 (during initiation)	Weeks 22–26 (mid-trial)	Weeks 48–52 (end of main phase)	Weeks 74–78 (end of extension phase)
Estimated treatment difference (95% confidence interval)	TAR _{>180 mg/dL}	2.34 (–1.09, 5.77) ^d	–3.69 (–6.03, –1.34) ^d	–4.58 (–6.99, –2.17) ^d	–4.65 (–7.20, –2.10) ^d
	TIR _{70–180 mg/dL}	–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 _{<70 mg/dL}	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 _{<54 mg/dL}	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.

^aAnalysis of variance model, with region and randomised treatment as fixed factors. ^cConfirmatory endpoint. ^dNegative 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

TIR (70-180 mg/dL) > 70%, TAR (180 mg/dL) < 25% and TBR (70 mg/dL) < 4%



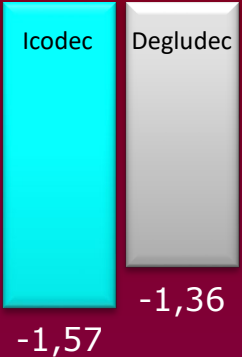
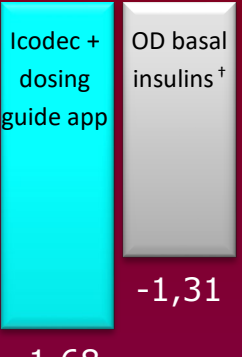
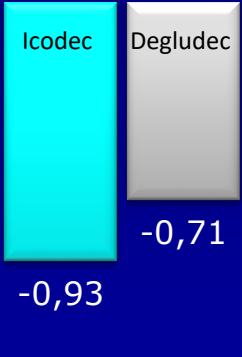
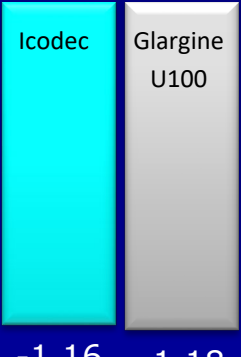
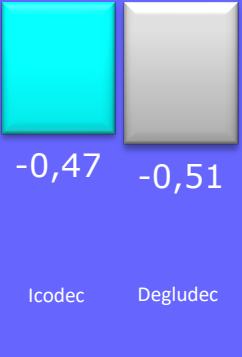
More participants achieved the triple composite endpoint of TIR >70%, TAR <25% and TBR (<3.9 mmol/L [70 mg/dL]) < 4% at weeks 22–26, 48–52 and 74–78 with icodec versus glargine U100

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).

^bOdds ratio (icodec/glargine U100) for weeks 0–4 was not calculated because it was not at steady state. ^cThe 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.

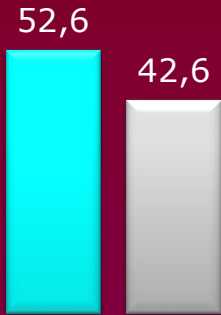
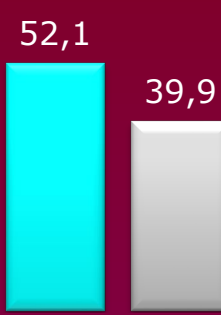
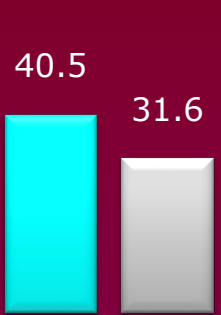
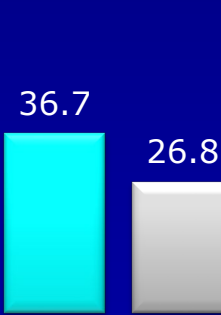
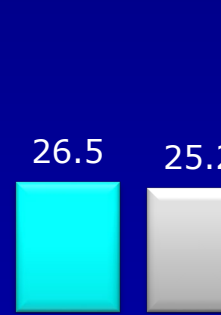
ONWARDS programme: primary endpoint

	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]; <i>p</i> <0.0001*; <i>p</i> =0.02**	ETD [95% CI]: -0.21% [-0.34 to -0.08]; <i>p</i> <0.001*; <i>p</i> =0.002**	ETD [95% CI]: -0.38% [-0.66 to -0.09]; <i>p</i> <0.0001*; <i>p</i> =0.009**	ETD [95% CI]: -0.22% [-0.37 to -0.08]; <i>p</i> <0.0001*; <i>p</i> =0.0028**	ETD [95% CI]: 0.02% [-0.11 to 0.15]; <i>p</i> <0.0001*	ETD [95% CI]: 0.05% [-0.13 to 0.23]; <i>p</i> =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: 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 HbA1c <7.0% 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.

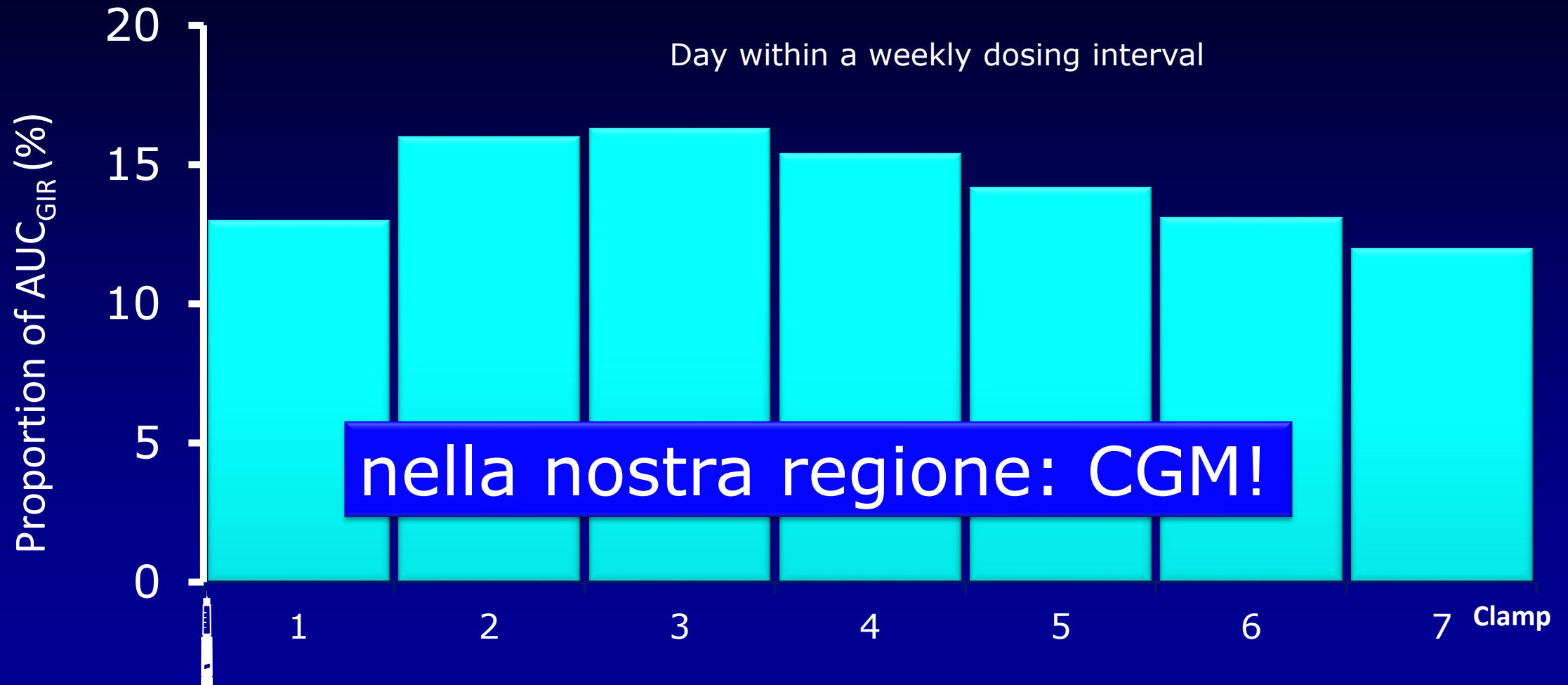
ONWARDS programme: hypoglycemia

	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)	0,3 0,16 Icodec Glargine U100	0,31 0,15 Icodec Degludec	0,19 0,14 Icodec + dosing guide app OD basal insulins[†]	0,73 0,27 Icodec Degludec	5,64 5,62 Icodec Glargine U100	19,93 10,37 Icodec Glargine U100
Endpoint assessed (week)	52	26	52	26	26	52
	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.

modelled glucose-lowering effect of icodec



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

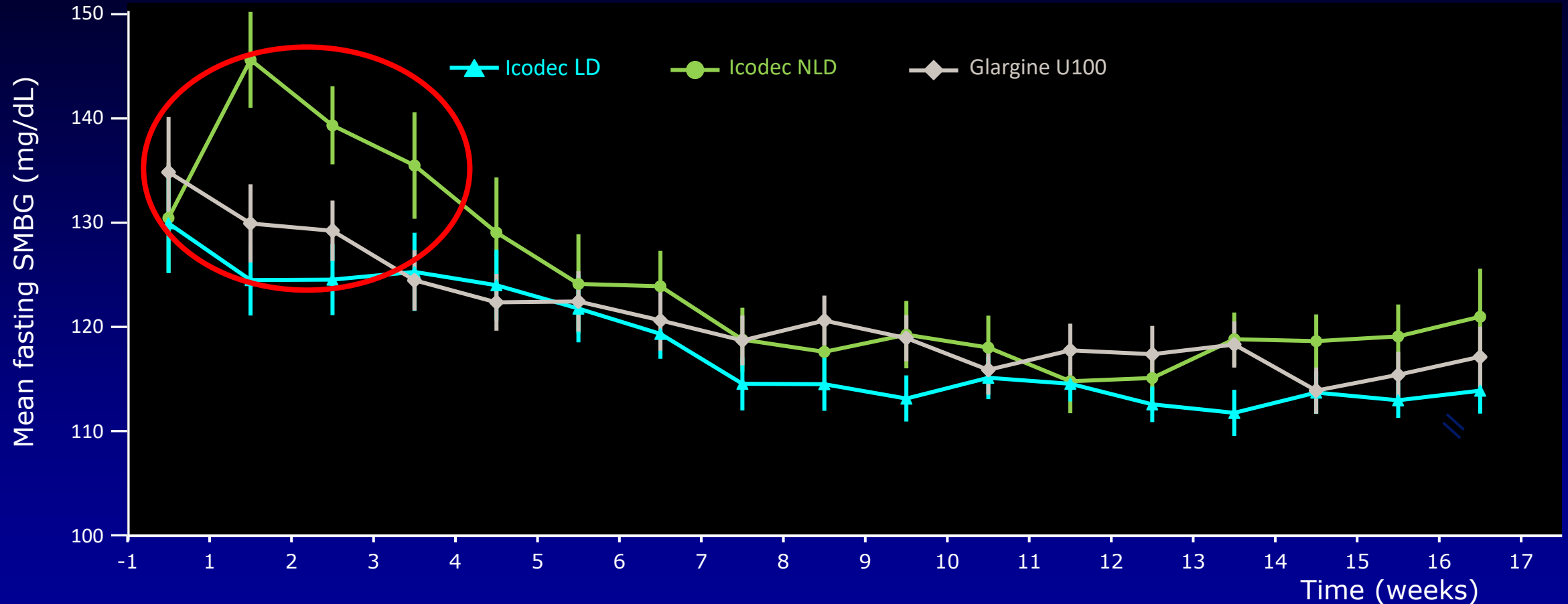
Modelled distribution of total glucose-lowering effect (AUC_{GIR}) of icodec within a dosing interval of one week at close to steady state. All three dose levels are combined. Individuals completing both glucose clamps and with pharmacokinetic data at steady state are included ($n=32$). Data are arithmetic 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).

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 $\pm$ 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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- **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.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- 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.

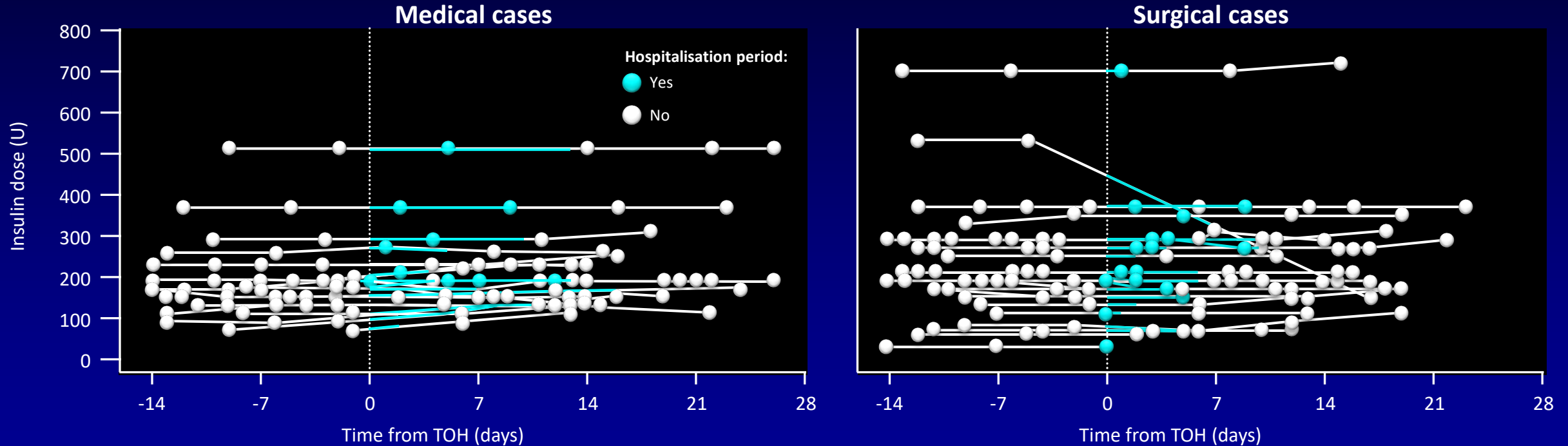
Diabetici di tipo 2 già in trattamento con insulina basale in difficoltà con la terapia quotidiana.

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

Icodec dose during and around hospitalisation

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

Example: ONWARDS 1 (T2D)



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. [Phillis-Tsimikas A et al. EASD 2023 Annual Meeting. SO-781.](#)

Webcare Lazio

Inserimento Prescrizione

Codice ISO

DPC233 - INSULINA ICODEC

Data Inizio Prescrizione

24/10/2025

Medico Prescrittore

GIACCARI ANDREA (01388) Endocrinologo POLICLINICO GEMELLI

Prima Prescrizione

- ☒ Sì
☐ No

Farmaco

051230124ICODEC*SC 1PEN 700U/ML 3ML+14A

Prescrizione

180 UI per 7 giorni per 48 settimane

Calcola

Cancella

Forma farmaceutica

SOLUZIONE INIETTABILE

Grammatura

2100UI

Q.ta per confezione

1



"700 UI/ml soluzione iniettabile, uso sottocutaneo" cartuccia (VETRO) in penna preriempita (FlexTouch) 1.5 ml, 1 penna preriempita + 14 (2 x 7) aghi

AIC n. 051230062/E (in base 10)

Classe di rimborsabilità

A

Prezzo ex-factory (IVA esclusa)

€ 77,31

Prezzo al pubblico (IVA inclusa)

€ 127,58

Q.ta in unità posologiche

Totale confezioni

Durata prescrizione in mesi

Numero confezioni mensile

possibili rischi legati ad alterazioni dell'albumina

- con 280 Unità di Icodec (pari a 40 Unità di basale giornaliera)
concentrazione raggiunta < 500 nmol/L
 - albumina ha concentrazione di ~ 0.4 g/L
con PM 69 kdalton corrisponde a ~ 580.000 nmol/L
 - ogni molecola di albumina ha 4 siti di legame con icodec
 - $580.000 * 4 = 2.320.000$ siti di legame
 $2.320.000$ siti di legame / 500 molecole di icodec = 4.640
- ~ 4.640 siti di legame per ogni singola molecola di icodec

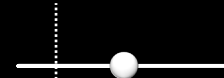
Diabetes Treatment Satisfaction Questionnaire (DTSQ)

a selection of answers in ONWARDS trials with icodec

DTSQ item

HR (95% CI)

satisfaction with current treatment



0.13 (-0.06 – 0.32)

convenience of treatment



0.28 (0.08 – 0.48)

flexibility of treatment



0.30 (0.10 – 0.49)

satisfaction with diabetes understanding



0.07 (-0.10 – 0.24)

willingness to recommend treatment to others



0.25 (0.08 – 0.42)

willingness to continue trial treatment



0.22 (0.04 – 0.40)

-0.5

0

0.5

1.0

better comparator

better icodec

ORIGINAL ARTICLE



Once-weekly administration of insulin in the real-world management of type 2 diabetes. A Delphi-like consensus

Riccardo Candido¹ · Raffaella Buzzetti² · Agostino Consoli³ · Concetta Irace⁴ · Enrico Torre⁵ · Roberto Trevisan⁶ · Gian Paolo Fadini^{7,8} · T2D once-Weekly Insulin Expert Panel Group

Received: 25 July 2025 / Accepted: 2 November 2025

© The Author(s) 2025

Once-weekly administration of insulin in the real-world management of type 2 diabetes. A Delphi-like consensus

15. Once-weekly basal insulin may contribute to promote **earlier initiation** of basal insulin therapy thus reducing therapeutic inertia. 100%

16. Once-weekly basal insulin reduces the impact of therapy on patients' **quality of life**. 100%

17. Once-weekly basal insulin could alleviate the workload for **caregivers** and healthcare professionals. 90.9%

22. While the efficacy of weekly basal insulin has been established in clinical trials, **real-world data** will be crucial in determining its true place in therapy, especially in diverse patient populations. 90.9%

24. All people living with type 2 diabetes requiring basal insulin are **potential candidates** for once-weekly basal insulin therapy. 90.9%

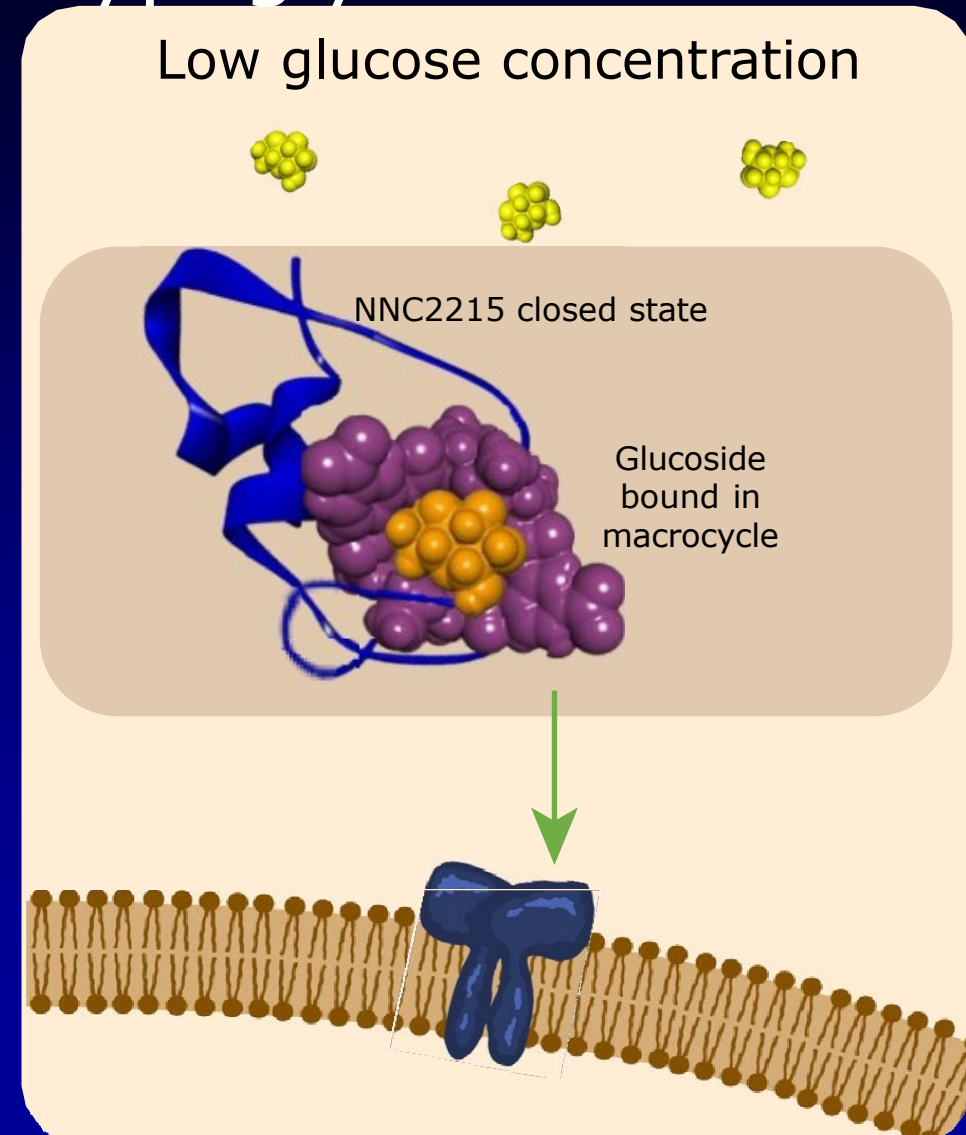
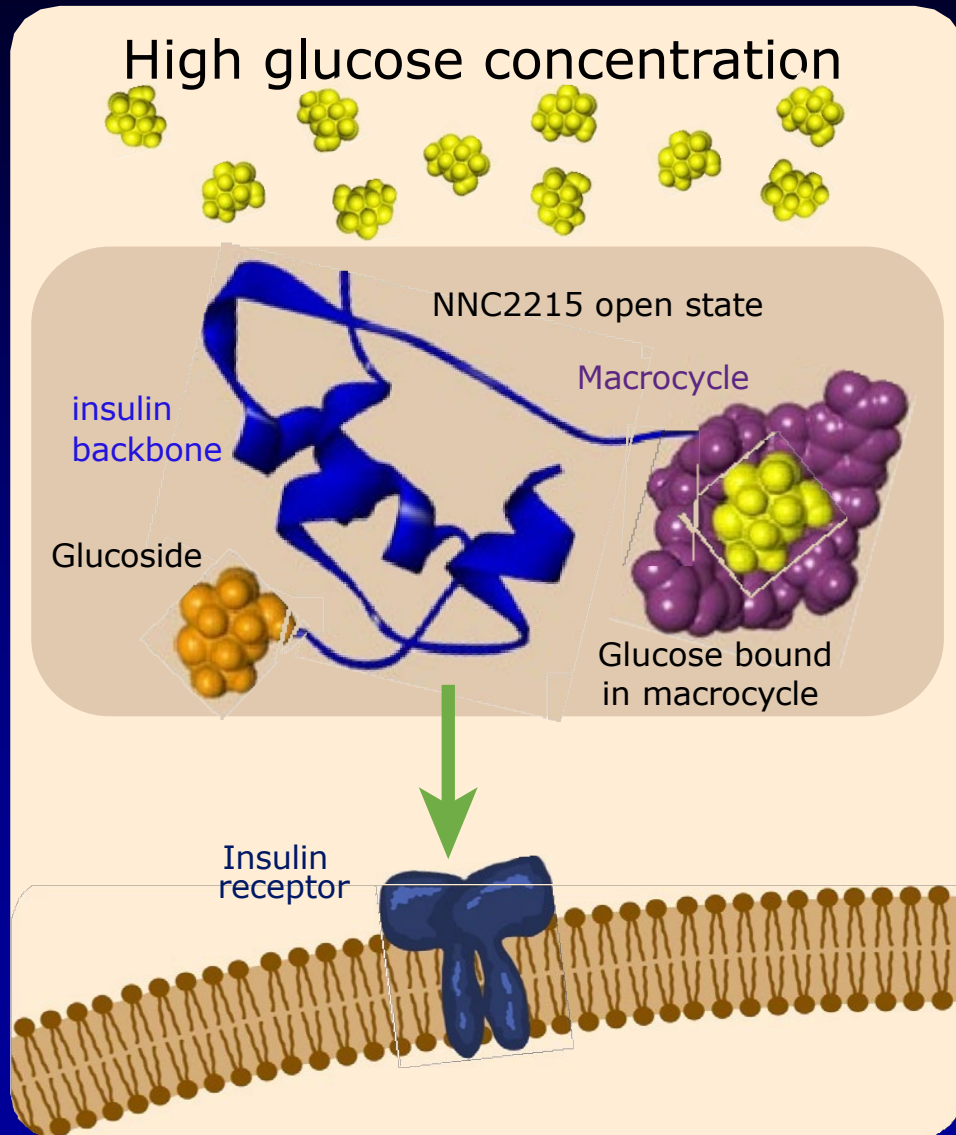
27. People living with diabetes who **struggle** with insulin administration, such as elderly patients supported by caregivers or those with particularly irregular lifestyles, are the **primary candidates** of once-weekly basal insulin therapy. 63.6%

31. The use of different titration algorithms, compared to second-generation basal insulins (degludec and glargine U300), poses a **challenge in the implementation** of once-weekly basal insulin therapy. 36.4%

36. The use of Continuous Glucose Monitoring (**CGM**) can be helpful in optimizing once-weekly insulin therapy. 63.6%

37. The use of dedicated **digital tools** can support accurate titration and help achieving glycemic targets. 81.8%

NNC2215: Glucose-sensitive insulin with attenuation of hypoglycaemia



Conclusioni

icodec permette di iniziare una terapia insulinica (nel diabete tipo 2) con estrema facilità.

Sia per diabetologo che, soprattutto, per paziente.

Non determina alcun aumento di rischio (a confronto con altre basali, anche per ipo).

l'importante è titolare (senza fretta)

ora sta a noi (basta inerzia!)