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La maneggevolezza degli analoghi insulinici di seconda e terza generazione

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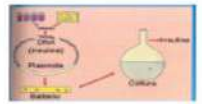
AOU Città della Salute e della Scienza di Torino

L’insulina ideale

Evoluzione della terapia insulinica

1921	1946	1979	Anni ‘90 e 2000
Isolamento dell’insulina	Insulina NPH	Insulina umana ricombinante	Analoghi rapidi e basali



“Nuova terapia insulinica”: le caratteristiche da soddisfare

- ✓ Efficacia
- ✓ Adeguata durata d’azione
- ✓ Ridotta variabilità d’azione
- ✓ Flessibilità
- ✓ Sicurezza
- ✓ Basso rischio ipoglicemico
- ✓ Buon rapporto costo-efficacia

Tempo

Criteri di valutazione

- Insulin Steady State
  - Dynamic equilibrium in insulin concentration within therapeutic limits between doses (us. to 3 to 5 half-lives)
- Controlled Accumulation
  - Depending on the half-life(t/2), the dose, the frequency
- Peak-to-Trough (P/T) ratio
  - Difference between the peak and the nadir concentrations
    - (rate of absorption, half-life, dosing interval)
  - High P/T ratio desirable for a given dose of rapid acting
  - Low P/T ratio desirable for basals
- Loading Dose/One Time Starting Dose
  - Initial one time dose used to shorten the time to reach the steady state

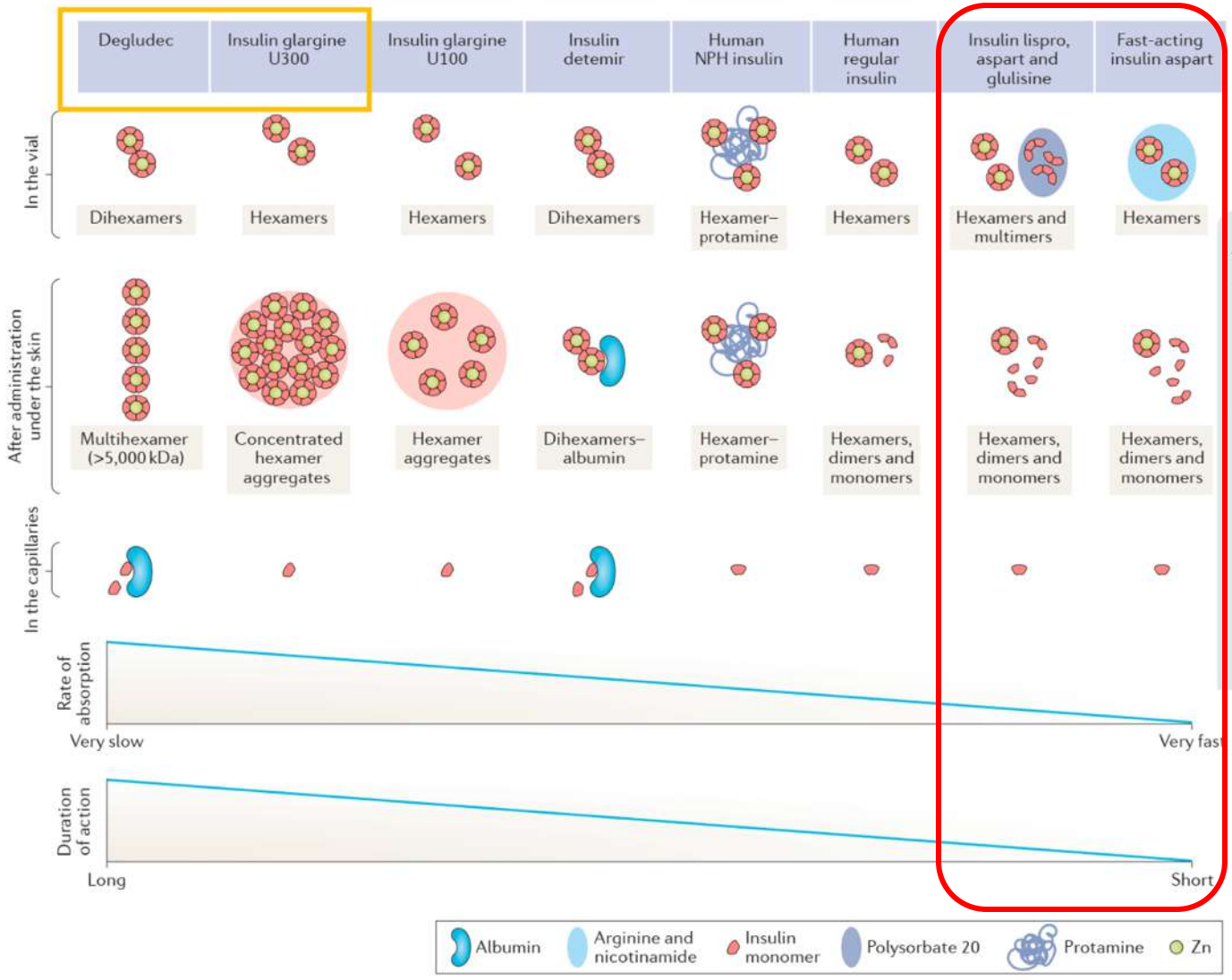
Physiological Basis for Insulin Replacement

- Structures and Structural Properties
  - Duration of action; day to day or within day absorption variability, hypo risk
- Signaling and Biology
- Whole Body Distribution
  - Hydrodynamic size; distribution in hepatic and parenchymal tissues
- Clearance
  - 30-80% kydney; binding to HSAalbumin
- Distribution Challenges
- Pharmacokinetic Variability

Caratteristiche dell'Insulina Basale Ideale

- Profilo farmacocinetico parafisiologico
- Farmacocinetica e farmacodinamica che minimizzano la variabilità intergiornaliera
- Gradiente fegato/periferia con basso rischio di iperinsulinizzazione epatica e basso rischio di ipoglicemia
- Bassa frequenza di iniezioni
- Semplicità di dose
- Risposta al cambiamento glicemico

Differente assorbimento e durata d'azione delle insuline umane vs gli analoghi



Key points

- Established rapid-acting and long-acting insulin analogues have enabled more patients with type 1 diabetes mellitus to reach better glucose targets, with lower hypoglycaemia rates and a better quality of life than was possible with short-acting and long-acting human insulin
- In patients who are prone to severe hypoglycaemia, using a full analogue regimen is rapidly cost saving and should therefore be the standard of care in all patients with type 1 diabetes mellitus
- The new long-acting insulin analogues insulin glargine U300 and insulin degludec have shown increased stability, which translates to a reduced risk of nocturnal hypoglycaemia and increased flexibility in timing of administration
- Faster and shorter acting insulin analogues are needed for use in insulin pumps and future 'artificial pancreas' systems; fast-acting insulin aspart, a new formulation of aspart, is well advanced in clinical development

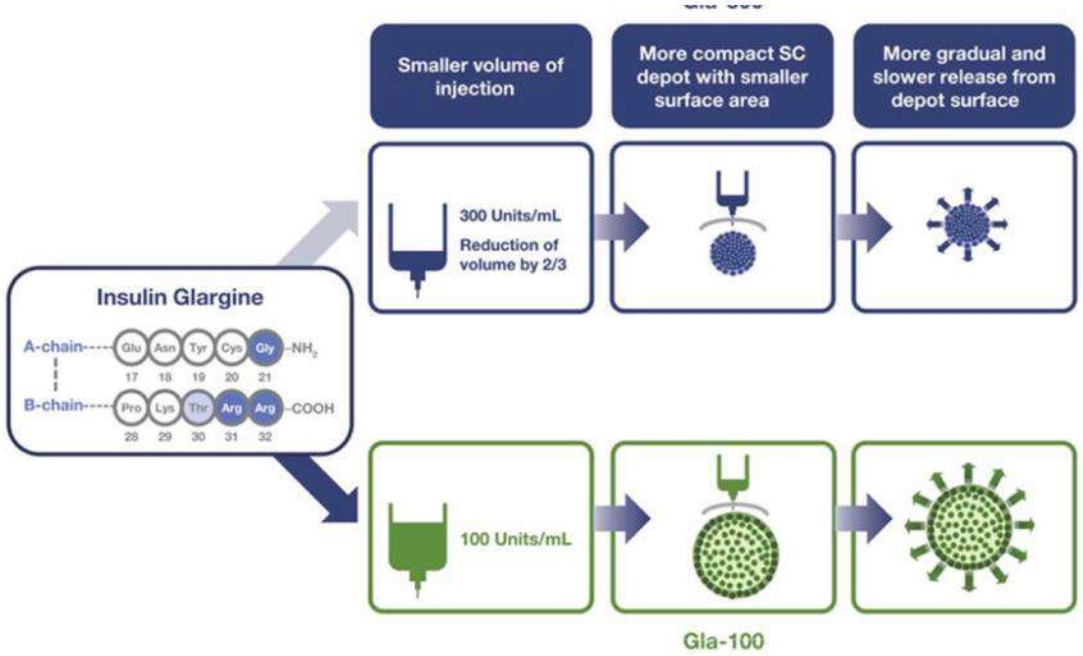
NATURE REVIEWS | ENDOCRINOLOGY 2017

Analoghi insulinici basali di Seconda Generazione

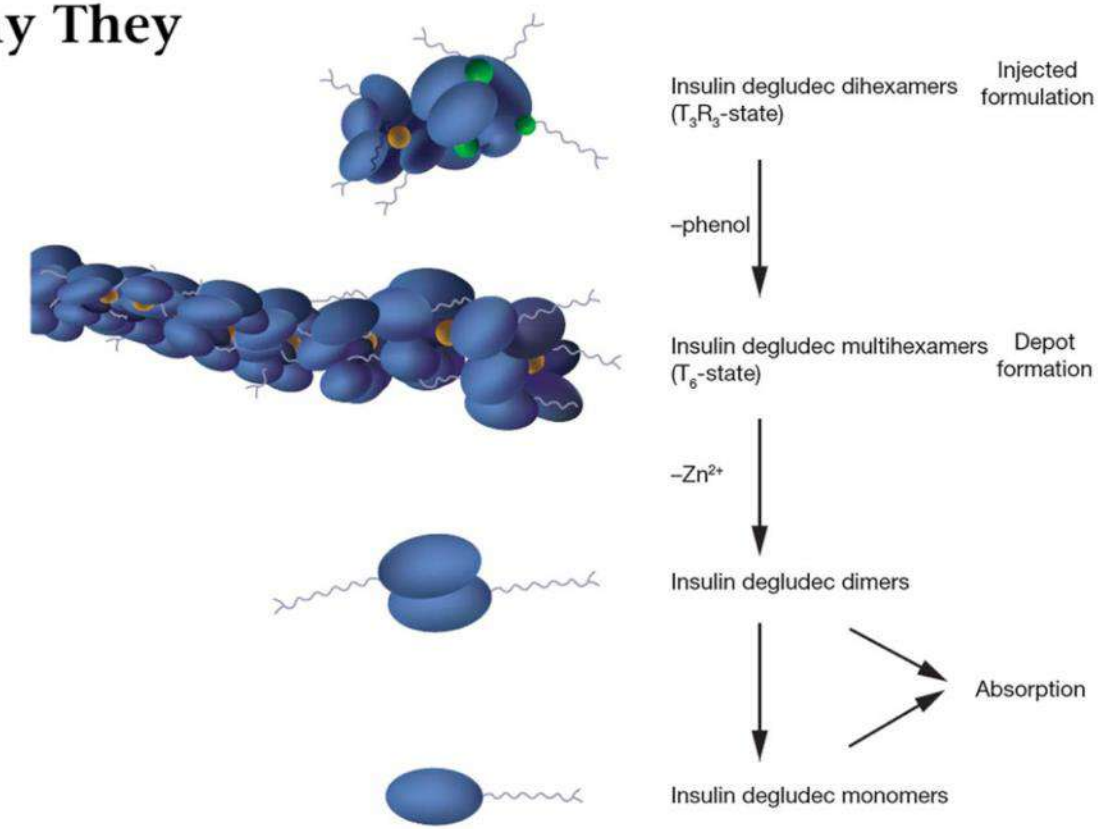
Insulina	Descrizione
Degludec	Analogo insulinico basale a lunga durata d'azione
Glargine U-300	Formulazione 3 volte concentrata di glargine U-100

- Le nuove insuline Degludec e Glargine U300 sono caratterizzate da una maggiore durata d'azione e una minore variabilità glicemica rispetto a Glargine U100

Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different



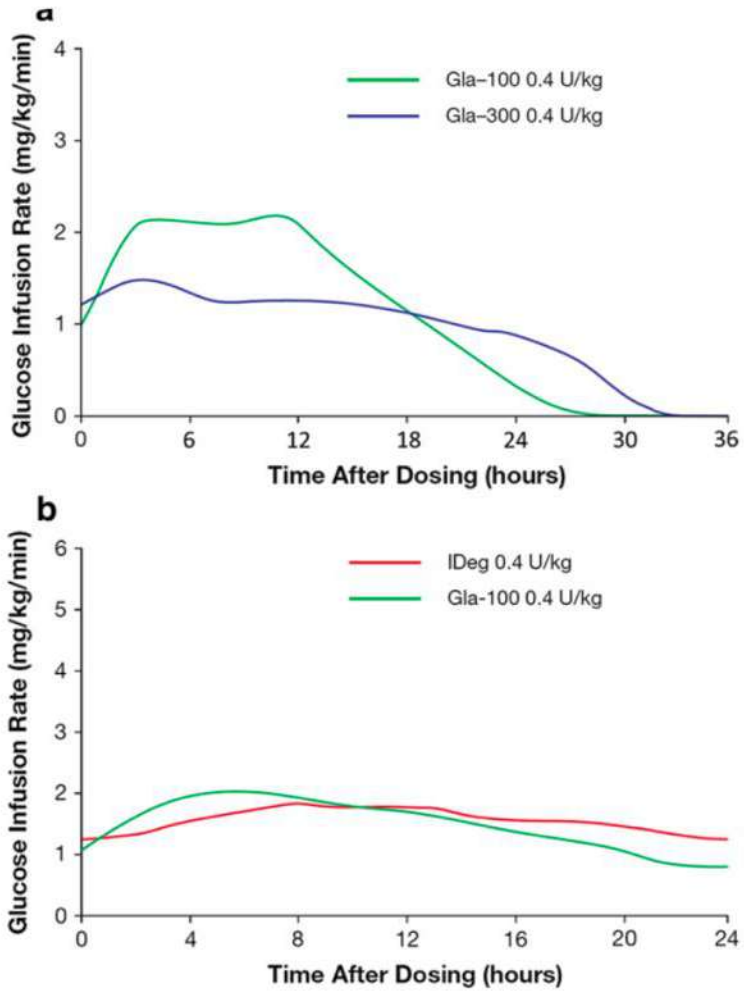
Gla-300 delivers the same dosage of insulin as Gla-100, but **in one-third of the volume**. This results in **reduced surface area** of injection depot, ultimately resulting in a **slower and more gradual release** of monomers of Gla-300 as compared with Gla-100.



- **IDeg** utilizes a **different method** of protraction

Adv Ther (2019) 36:1018–1030

Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different

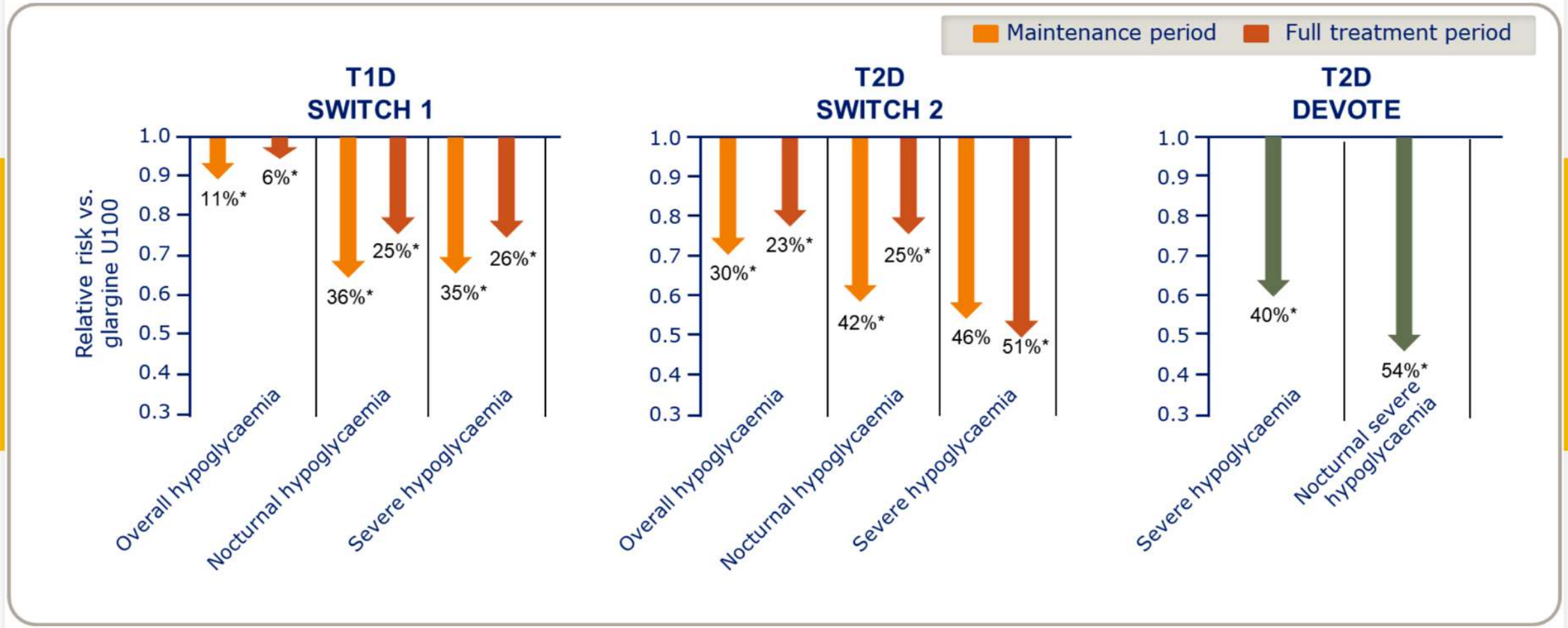


CONCLUSIONS

The time–action profile of an insulin preparation is determined by its time course and pattern of absorption and distribution from the subcutaneous injection site. Basal insulins have distinct mechanisms of protraction that give rise to equally distinct PK/PD profiles and accompanying clinical properties in people with T1D and T2D. Understanding these differential mechanisms is important to explain the clinical benefits and differences of the second-generation basal insulin analogs Gla-300 and IDeg over the earlier generation of basal insulins, Gla-100 and IDet. Gla-300 and IDeg show longer duration of action and smoother PK/PD profiles than these earlier-generation basal insulin analogs, leading to smaller glycemic excursions and a lowered risk of hypoglycemia, while retaining similar levels of glycemic control. Understanding the differences among first- and second-generation basal insulin analogs aids healthcare providers in making the most appropriate treatment decisions to address individual patient needs.

Adv Ther (2019) 36:1018–1030

Insulina Degludec vs Insulina Glargine 100: riduzione delle ipoglicemie



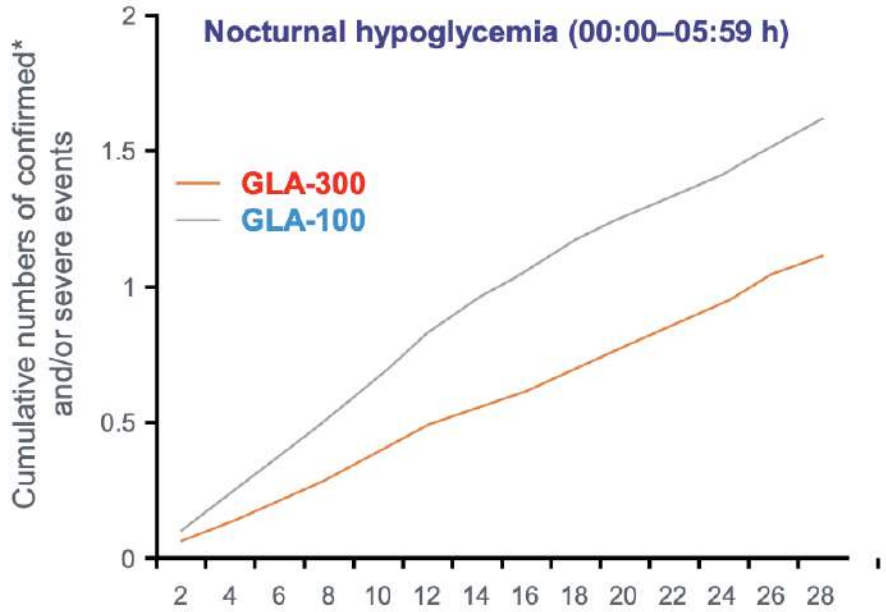
*Significant difference. Overall hypoglycaemia: severe or BG-confirmed hypoglycaemia; nocturnal hypoglycaemia, severe or BG-confirmed hypoglycaemia occurring between 00:01 am and 05:59 am, both inclusive; severe hypoglycaemia, an episode requiring third-party assistance and external adjudication

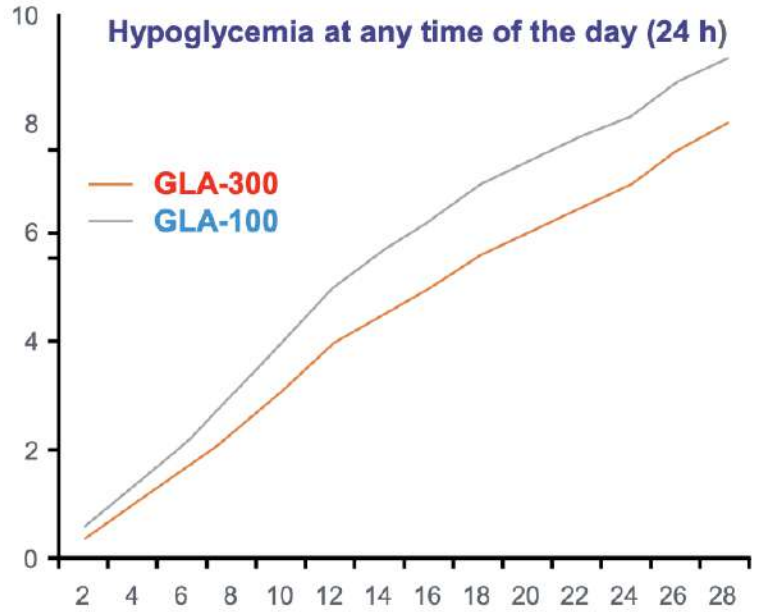
BG, blood glucose; glargine U100, insulin glargine 100 units/mL; T1D, type 1 diabetes; T2D, type 2 diabetes

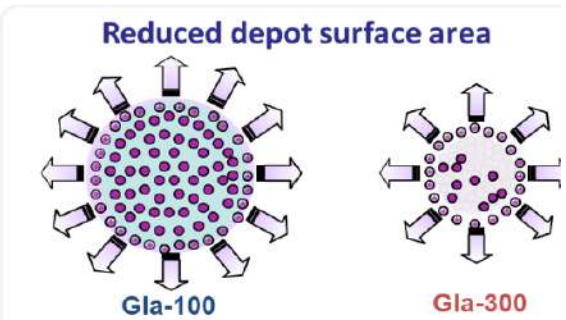
Lane *et al. JAMA* 2017;318:33–44; Wysham *et al. JAMA* 2017;318:45–56; Marso *et al. N Engl J Med* 2017;377:723–32

Minori ipoglicemie diurne e notturne con Glargine 300

EDITION 1-2-3 T2DM Pooled Analysis







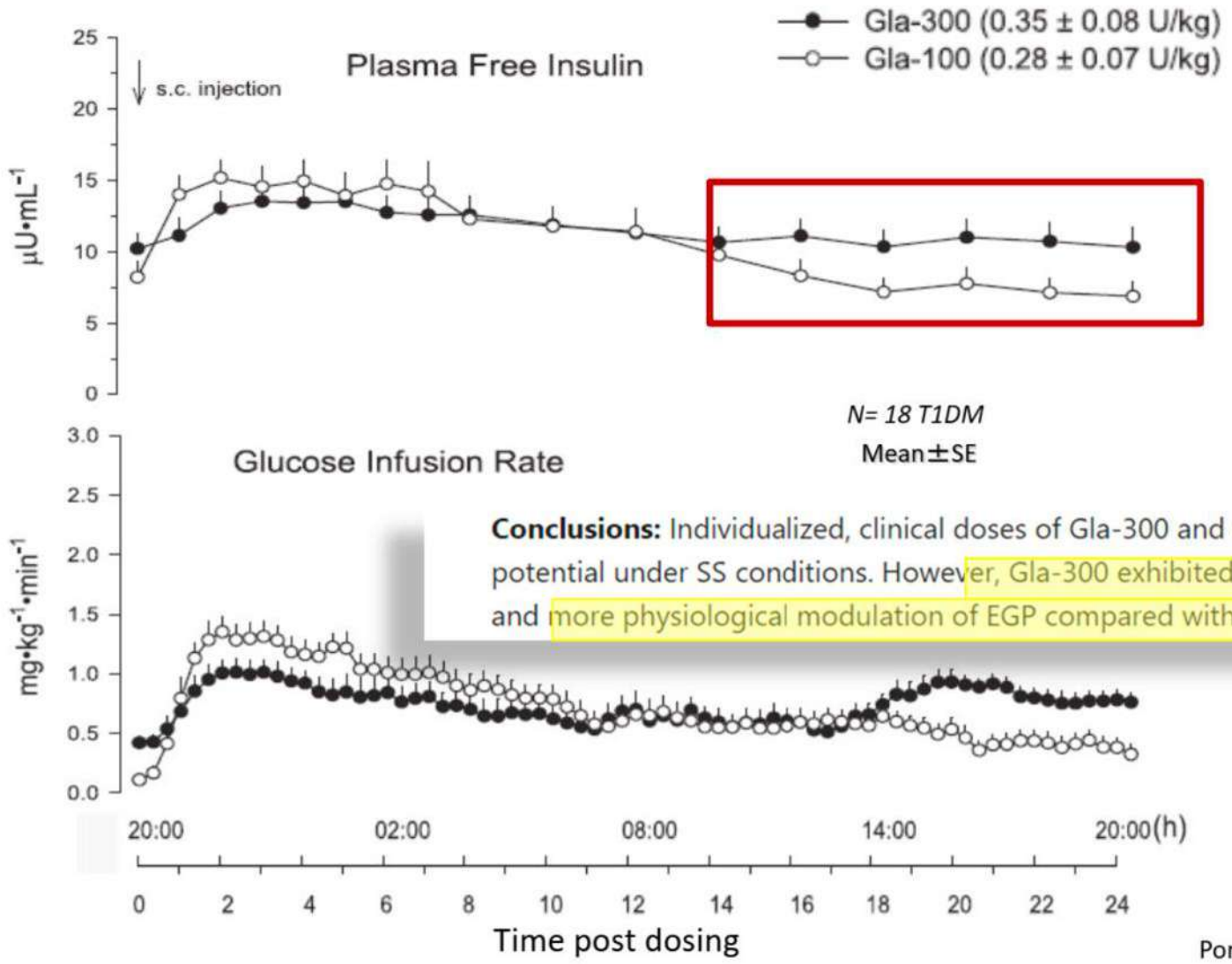
La riduzione del volume diminuisce la superficie depot, con un rallentato tasso di cessione di glargine

	GLA-300	GLA-100	
Rate per patient-year	2.10	3.06	-31%
RR (95% CI) vs U100	**0.69** (0.57 to 0.84)		
P value	**0.0002**		

	GLA-300	GLA-100	
Rate per patient-year	**15.22**	17.73	-14%
RR (95% CI) vs U100	**0.86** (0.77 to 0.97)		
P value	**0.0116**		

*Confirmed events based on plasma glucose ≤3.9 mmol/L (≤70 mg/dL)

PK-PD of Gla-300 and Gla-100 at Clinical Doses



Conclusions: Individualized, clinical doses of Gla-300 and Gla-100 resulted in a similar euglycemic potential under SS conditions. However, Gla-300 exhibited a more stable profile, with lower variability and more physiological modulation of EGP compared with Gla-100.

Porcellati F. et al., Diabetes Care 2019

Real-World Effects of Second-Generation Versus Earlier Intermediate/Basal Insulin Analogues on Rates of Hypoglycemia in Adults with Type 1 and 2 Diabetes (iNPHORM, US)

Table 4 Population-average adjusted hypoglycemia rate ratios comparing second-generation to earlier intermediate/basal insulin analogue use, by type of diabetes, event severity, and timing

Type of hypoglycemia	Estimated population-average adjusted rate ratios (95% CI)					
	All (n = 413)		T1DM (n = 81)		T2DM (n = 332)	
Non-severe		p-value		p-value		p-value
Overall	0.81 (0.68–0.97)	0.02*	0.85 (0.62–1.17)	0.33	0.81 (0.66–1.00)	0.05
Daytime	0.91 (0.76–1.10)	0.32	0.94 (0.67–1.31)	0.72	0.92 (0.73–1.15)	0.45
Nocturnal	0.57 (0.44–0.74)	< 0.001*	0.52 (0.34–0.81)	0.003*	0.63 (0.46–0.86)	0.004*
Severe		p-value		p-value		p-value
Overall	0.87 (0.65–1.16)	0.35	0.52 (0.26–1.07)	0.07	0.97 (0.70–1.36)	0.88
Daytime	0.98 (0.71–1.36)	0.91	0.60 (0.27–1.33)	0.21	1.10 (0.76–1.59)	0.60
Nocturnal	0.56 (0.35–0.90)	0.02*	0.23 (0.06–0.93)	0.04*	0.63 (0.38–1.06)	0.08

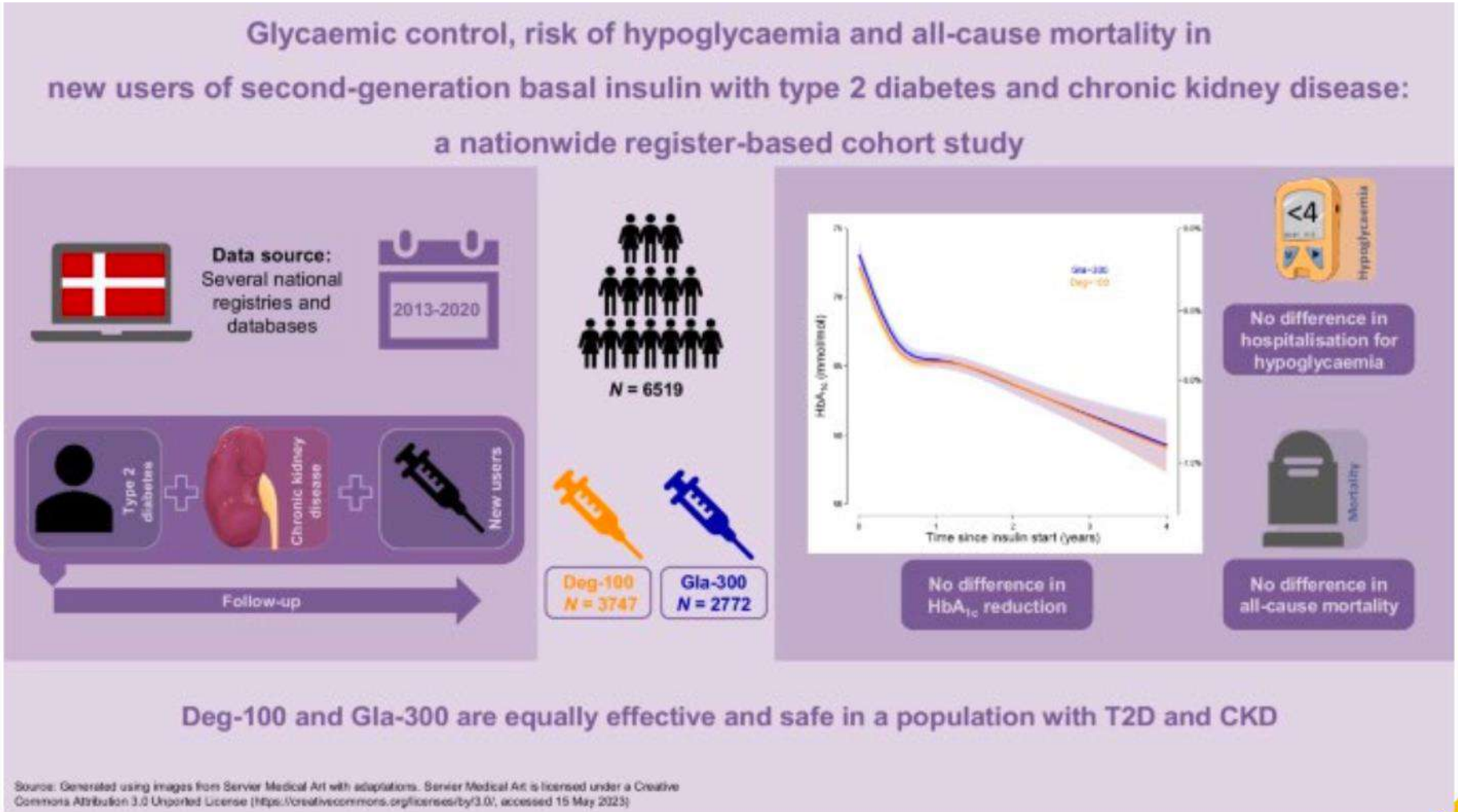
Diabetes Ther (2023) 14:1299–1317

This study evaluates the impact of second-generation insulins (insulin degludec and glargine U-300) versus earlier intermediate and basal insulins (NPH, insulin glargine U-100 and detemir, premixed and fixed-ratio [FRC] insulins) on rates of overall, daytime, and nocturnal non-severe and severe hypoglycemia

What was learned from the study?

The most salient effects were observed for nocturnal hypoglycemia. Overall, second-generation insulin versus earlier intermediate/basal insulin users reported a 43% reduction in non-severe nocturnal hypoglycemia ($p < 0.001$) and a 44% reduction in severe nocturnal hypoglycemia ($p = 0.02$). These trends persisted across diabetes types

Among patients with either type 1 or 2 diabetes mellitus on basal insulin (with or without bolus), the use of second-generation basal insulins over earlier formulations should be prioritized whenever possible



Conclusions/interpretation We found no difference in HbA_{1c} reduction, hospitalisation for hypoglycaemia or all-cause mortality between Gla-300 and Deg-100 in a real-world population of new users with type 2 diabetes and moderate to end-stage chronic kidney disease. Therefore, we conclude that these two treatment options are equally effective and safe in this vulnerable population.

Diabetologia Published online: 28 July 2023

Motivazione della raccomandazione

Vi sono numerose evidenze provenienti da trial clinici che mostrano come l'uso degli analoghi lenti dell'insulina a maggiore durata di azione si associ ad un rischio minore di ipoglicemie totali e notturne e ad una tendenziale riduzione degli eventi ipoglicemici severi a parità di controllo metabolico e senza aumenti di peso corporeo.

La qualità delle evidenze è moderata, in particolare per il disegno in aperto della maggior parte degli studi inclusi e per la presenza di elevata eterogeneità per alcuni degli *outcome* critici.

Gli studi di farmacoeconomia mostrano che le nuove formulazioni hanno costi diretti maggiori; tuttavia, il rapporto costo-efficacia è generalmente favorevole per QALY guadagnati e per gli effetti positivi su rischio ipoglicemico. La disponibilità di biosimilari con costi diretti ridotti può ulteriormente migliorare il rapporto costo-efficacia.

AMD 1974 ASSOCIAZIONE MEDICI DIABETOLOGI

SID Società Italiana di Diabetologia

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

Considerazioni sull'implementazione

Gli analoghi lenti sono già considerati in Italia lo *standard of care*[7,8]. La prescrizione di analoghi lenti a maggiore durata di azione dovrebbe essere incoraggiata e gradualmente sostituita a quelli a minore durata di azione indipendentemente dal controllo glicemico. I medici di medicina generale e gli specialisti dovrebbero essere informati sui contenuti di questa raccomandazione attraverso specifici corsi di educazione continua in medicina.

Raccomandazione forte a favore dell'intervento, con qualità delle prove moderata

Si raccomanda l'uso degli analoghi lenti dell'insulina a maggiore durata di azione, rispetto a quelli a minore dura di azione, per tutti i pazienti con diabete di tipo 2 che necessitano di insulina basale.

Once-weekly vs. once-daily insulin therapy

Clinical

- Improved (or similar) glycaemic control with low hypoglycaemia risk
- Reduced treatment burden
- Easier to overcome clinical inertia

Molecular

- Longer half-life
- More stable PK/PD
- Slower clearance rate

Better treatment acceptance and adherence

Diabetes Obes Metab. 2023;

Currently explored technologic approaches to increase half-life of basal insulin

Insulin Icodec [1]

Acylated insulin: 20-carbon fatty diacid sidechain

High albumin binding

Reduced enzymatic degradation

Reduced insulin receptor-mediated clearance

Time-action profile ($t_{1/2}$ = approx. 8 days) supports once-weekly dosing in humans

Currently in Phase 3 Trials

Basal Insulin Fc [2]

Novel single-chain variant of insulin fused to human IgG Fc domain

Homo-dimer

Reduced insulin receptor potency with full agonism

Time-action profile ($t_{1/2}$ = approx. 17 days) supports once-weekly dosing in humans[3]

Currently in Phase 2 Trials

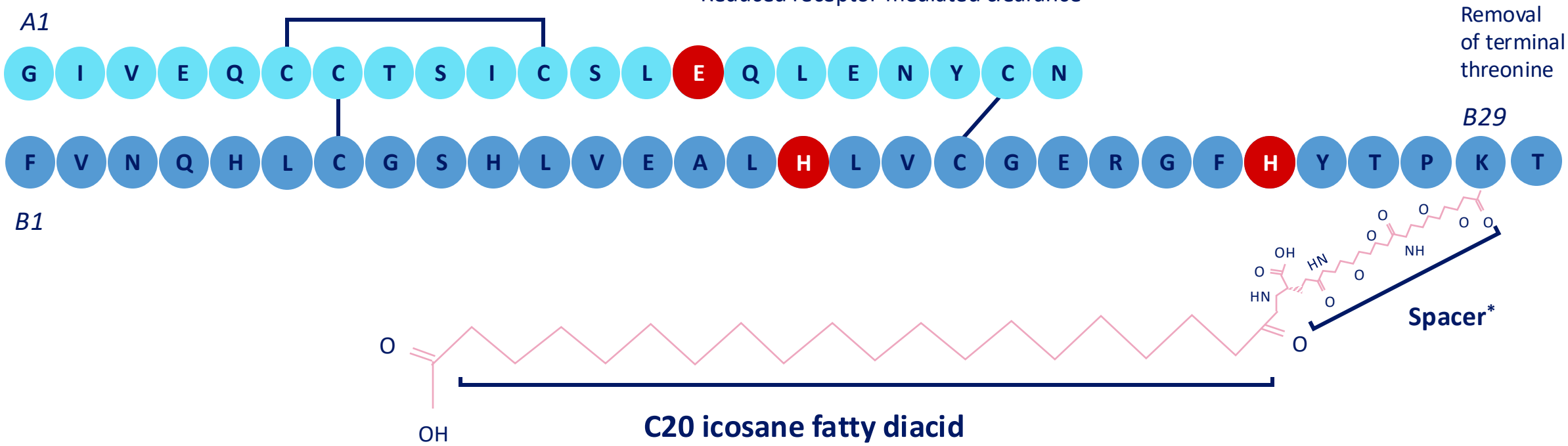
1. Moyers J et al. Preclinical Characterization of Once Weekly Basal Insulin Fc (BIFJournal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021, Page A442, https://doi.org/10.1210/jendso/bvab048.903; 2. Heise T et al. Basal Insulin Fc (BIF), A Novel Insulin Suited For Once Weekly Dosing For The Treatment of Patients With Diabetes Mellitus, Journal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021, Page A329, https://doi.org/10.1210/jendso/bvab048.672.

Insulin icodec

Designed to achieve a long half-life by changes to the human insulin molecule

Three amino acid substitutions

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



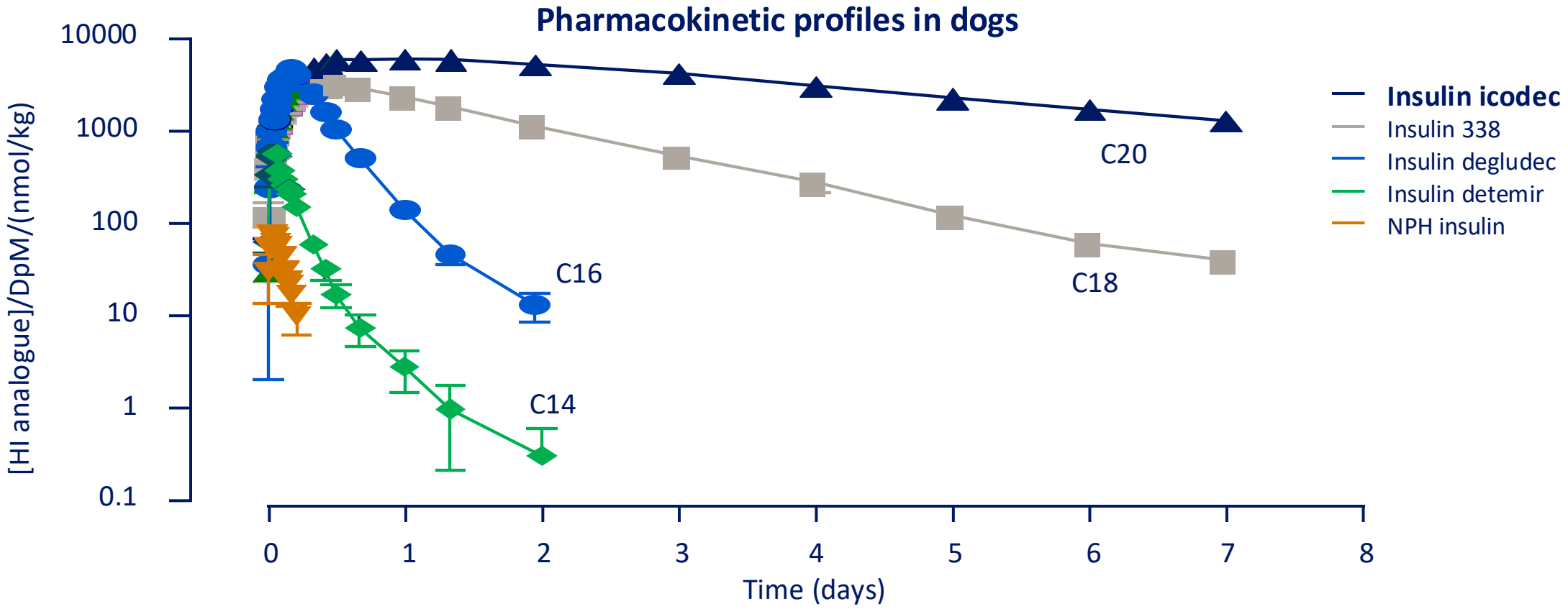
C20 icosane fatty diacid

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

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

Molecular Engineering of Insulin Icodec, the First Acylated Insulin Analog for Once-Weekly Administration in Humans Thomas B Kjeldsen. . 2021 Jul 8;64(13):8942-8950. doi: 10.1021/acs.jmedchem.1c00257. Epub 2021 May 4; Molecular and pharmacological characterization of insulin icodec: a new basal insulin analog designed for once-weekly dosing Erica Nishimura 1. BMJ 2021 Aug;9(1):e002301.

Preclinical studies show increased albumin binding with icodec gives longer half-life



	detemir	degludec	Icodec
fatty acid chain	miristic acid (C14)	hexadecanoic diacid (C16)	icosane (C20)
half life	5 - 7 h	25.4 h	196 h

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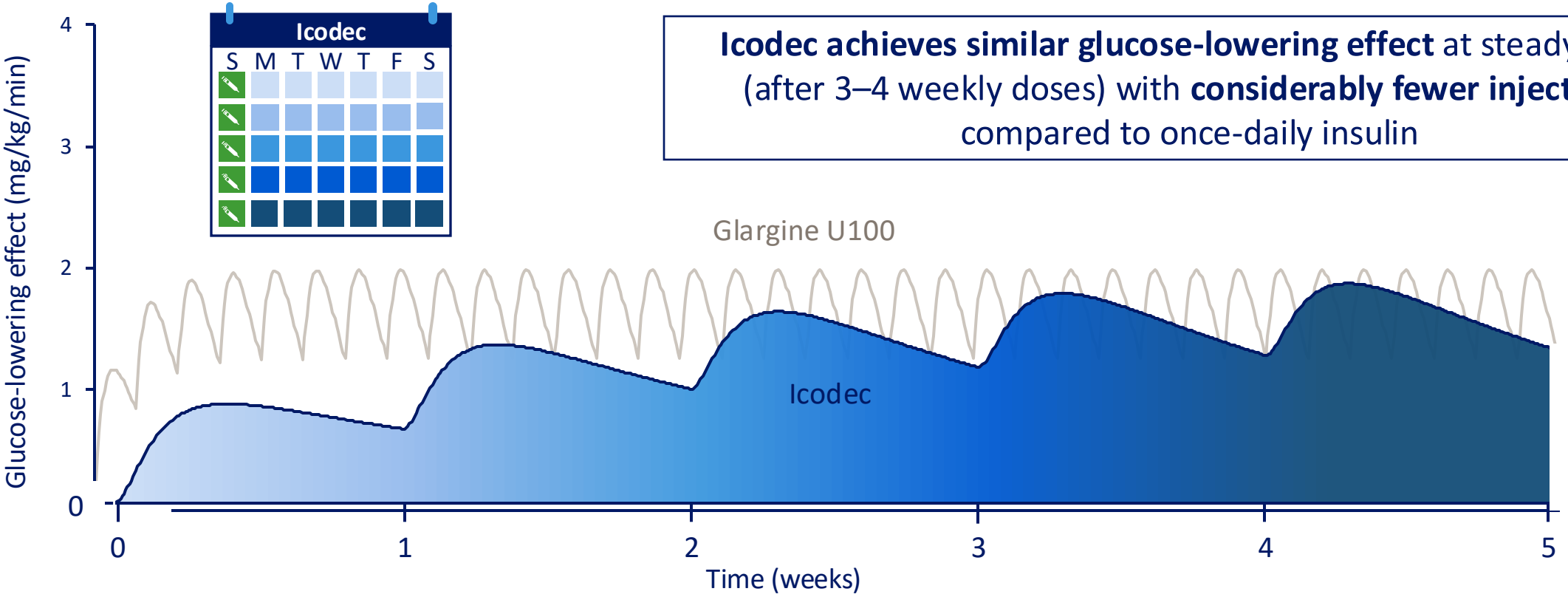
1. Nishimura E et al. 2020 ADA Scientific Sessions 236–OR.

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

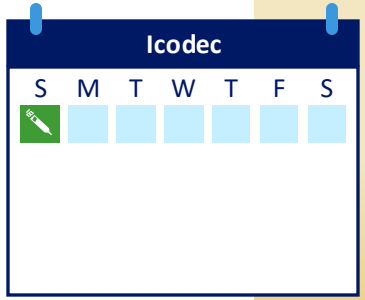
Simulated glucose-lowering effects at comparable insulin dose levels of icodec and glargine U100 (equivalent to 0.4 U/kg/day for both). U, unit(s).

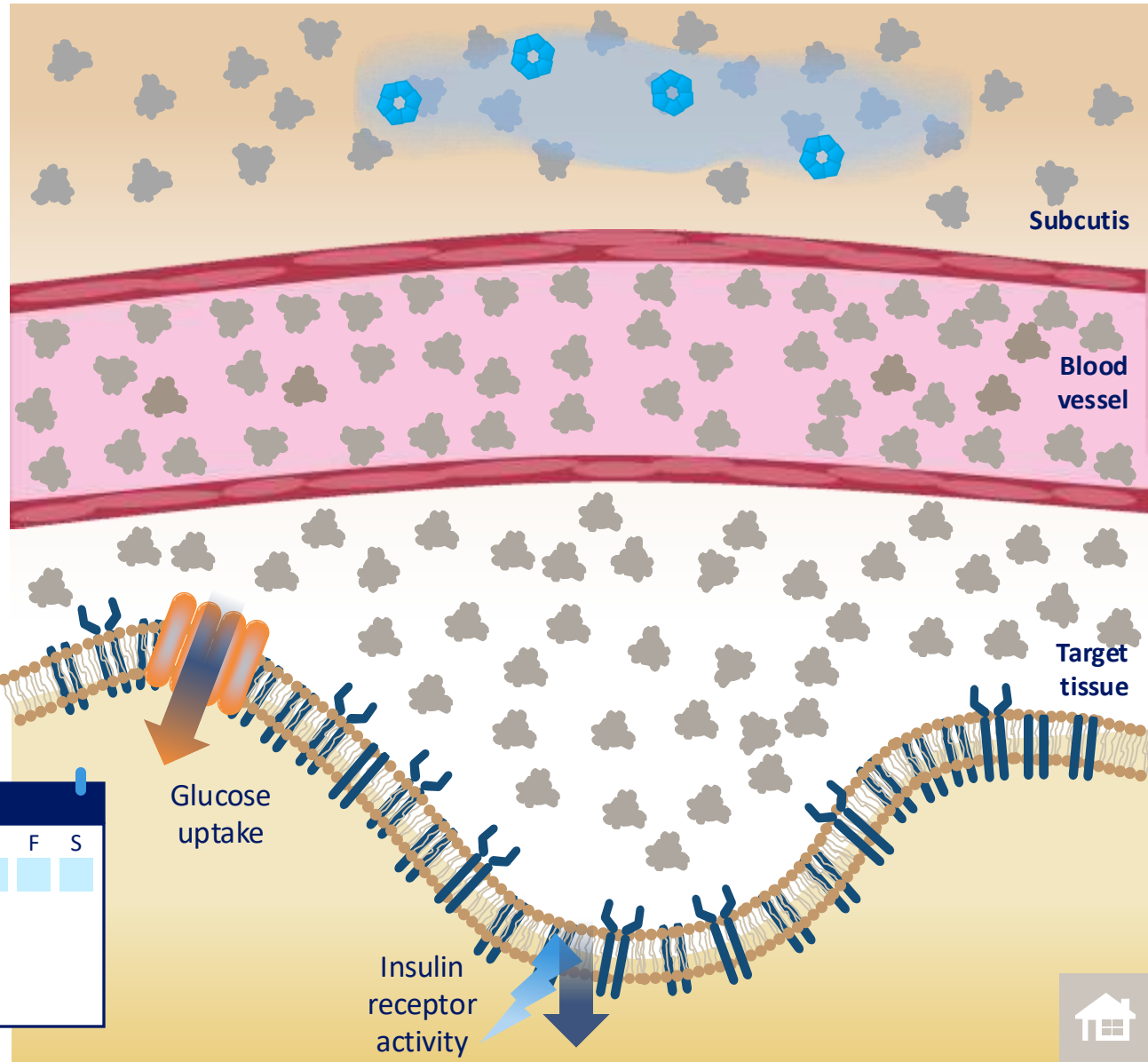
1. Nishimura E. Expanding horizons of treating diabetes: Looking into newer possibilities. Lecture presented at 14th National Insulin Summit 2020; December 12, 2020. https://vimeo.com/489887511. Accessed 11 Jun 2021.

The first injection

Icodec mode of action

- The formulation (700 U/mL) ensures the injection volume is similar to once-daily insulin
- After injection, hexamers slowly dissociate into monomers and **bind to albumin**
- Although a week's worth of insulin is administered, almost all icodec is albumin-bound **to form an inactive depot**
- Slowly, a small fraction of icodec reaches the insulin receptors at target tissues to stimulate glucose lowering





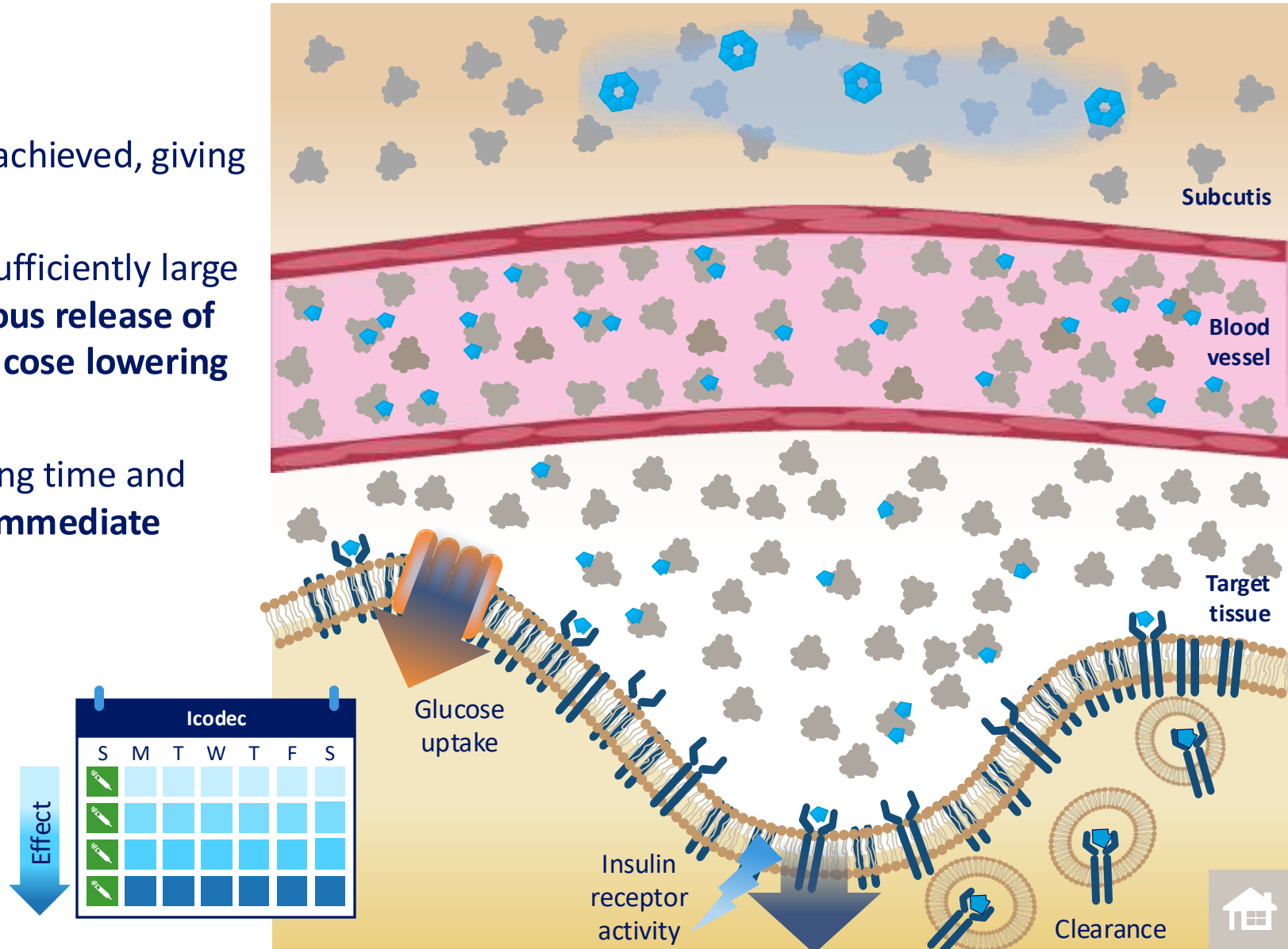
U, unit(s).

1. Nishimura E et al. 2020 ADA Scientific Sessions 236–OR.

At steady state

Icodec mode of action

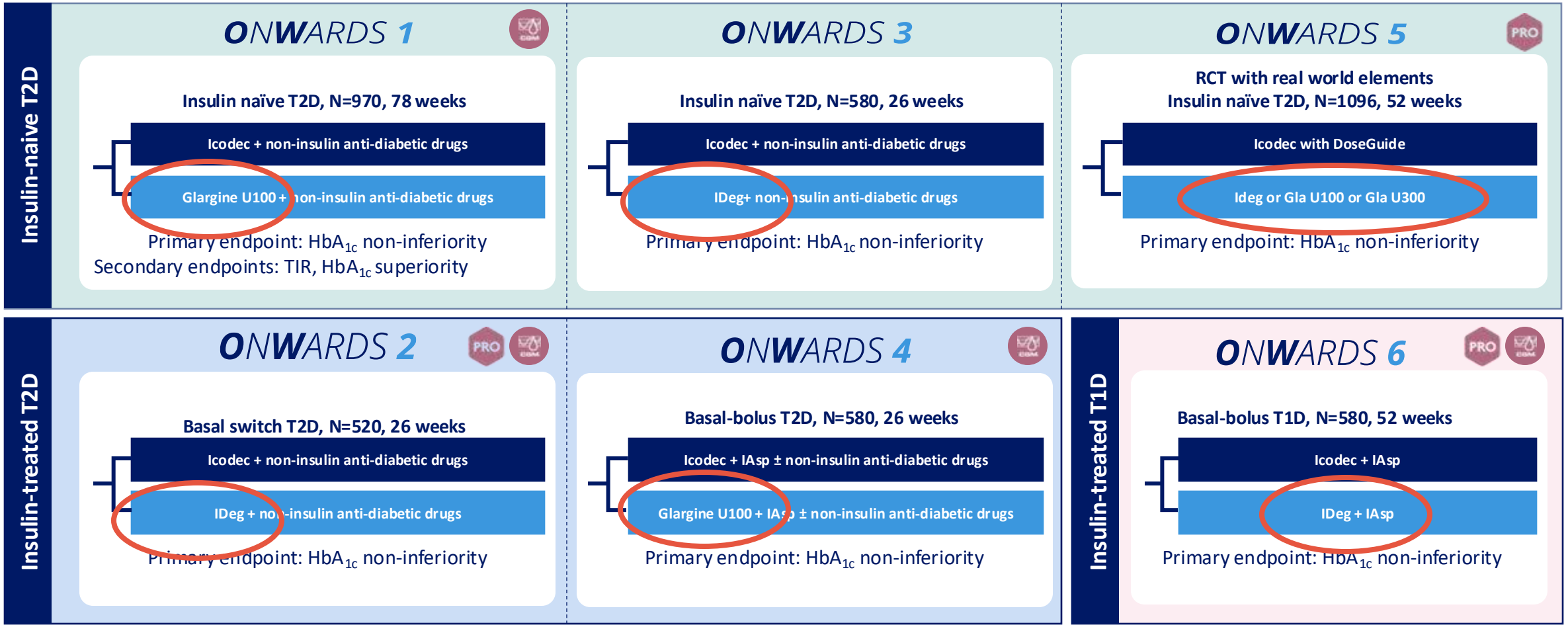
- After 3–4 injections, steady state* is achieved, giving **the full effect of the icodec dose**
- The icodec albumin-bound depot is sufficiently large enough to provide **slow and continuous release of active icodec to achieve effective glucose lowering throughout the week**
- At steady state, any variations in dosing time and amount lead to **minimal changes in immediate glucose-lowering effects** due to the slow release of icodec



*When the number of molecules dosed = number of molecules cleared. For illustrative purposes the albumin to icodec ratio have been considerably exaggerated (eg, in reality, at steady state, ~2000:1 albumin:icodec molecules).

1. Nishimura E et al. 2020 ADA Scientific Sessions 236–OR.

Overview ONWARDS programme



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

ONWARDS 1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 27, 2023 VOL. 389 NO. 4

Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin

Julio Rosenstock, M.D., Stephen C. Bain, F.R.C.P., Amoolya Gowda, M.D., Esteban Jódar, M.D., Ph.D., Bo Liang, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Tomoyuki Nishida, M.Sc, Roberto Trevisan, M.D., Ph.D., and Ofri Mosenzon, M.D., for the ONWARDS 1 Trial Investigators*

Trial number: NCT04460885

Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

Methods

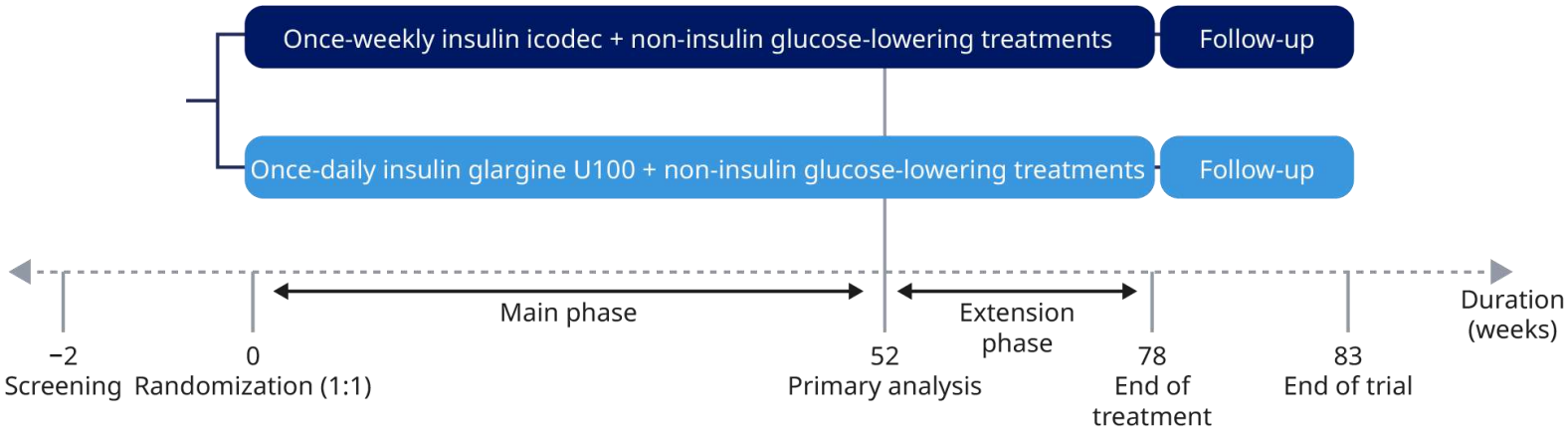
Trial design

- A 78-week, randomized, open-label, treat-to-target, phase 3a trial
- Participants were randomized 1:1 to receive once-weekly icodec or once-daily glargine U100

984 randomized participants

- Insulin-naive adults (≥ 18 years old) with T2D
- HbA_{1c} of 7.0–11.0% (53.0–96.7 mmol/mol)
- Body mass index of ≤ 40 kg/m^2 at screening

Supplementary Figure S1. Trial design



Adapted from manuscript Figure S1
ONWARDS 1 was conducted at 143 sites in 12 countries (Croatia, India, Israel, Italy, Japan, Mexico, Poland, Russia, Slovakia, Spain, the UK and the USA). Pretrial non-insulin glucose-lowering treatments were continued after randomization, except for sulfonylureas and glinides, which were discontinued. Continuous glucose monitoring profiles were collected intermittently at the following time points: randomization to week 4; week 22 to week 26; week 48 to week 52; week 74 to week 78; and in the follow-up period (week 78 to week 83)
Glargine U100, insulin glargine U100; HbA_{1c}, glycated hemoglobin; icodec, insulin icodec; T2D, type 2 diabetes

Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

Methods

Treatment titration

Starting dosages: 70 U/week for icodec and 10 U/day for glargine U100

Pre-breakfast SMBG[a]		Icodec dosage adjustment (U/week)	Glargine U100 dosage adjustment (U/day)
Up-titration	**Mean of SMBG values > 130 mg/dL** (> 7.2 mmol/L)	**+20**	**+3**
Target	**Mean of SMBG values in the range 80–130 mg/dL** (4.4–7.2 mmol/L)	**0**	**0**
Down-titration	**Lowest SMBG value < 80 mg/dL** (< 4.4 mmol/L)	**–20**	**–3**

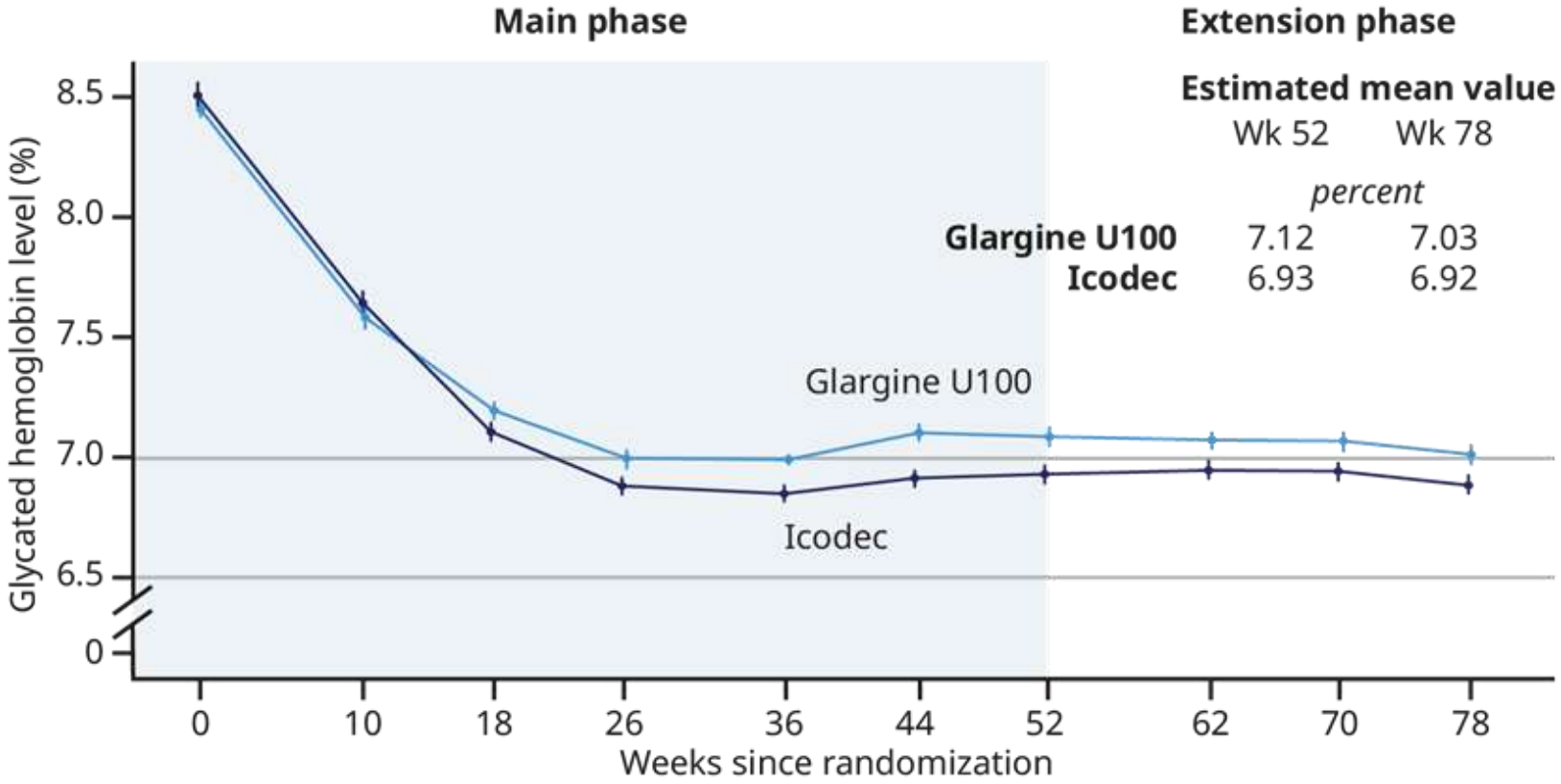
Insulin doses were titrated weekly to achieve a pre-breakfast SMBG target of 80–130 mg/dL (4.4–7.2 mmol/L)[a]

Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

Results

Change in HbA_{1c} from baseline

- Estimated mean change in HbA_{1c} from baseline to week 52 was −1.55%-points with icodec and −1.35%-points with glargine U100 (ETD [95% CI]: −0.19 [−0.36, −0.03] %-points)
- Noninferiority (P < 0.001) and **superiority** (P = 0.02) of icodec to glargine U100 were confirmed



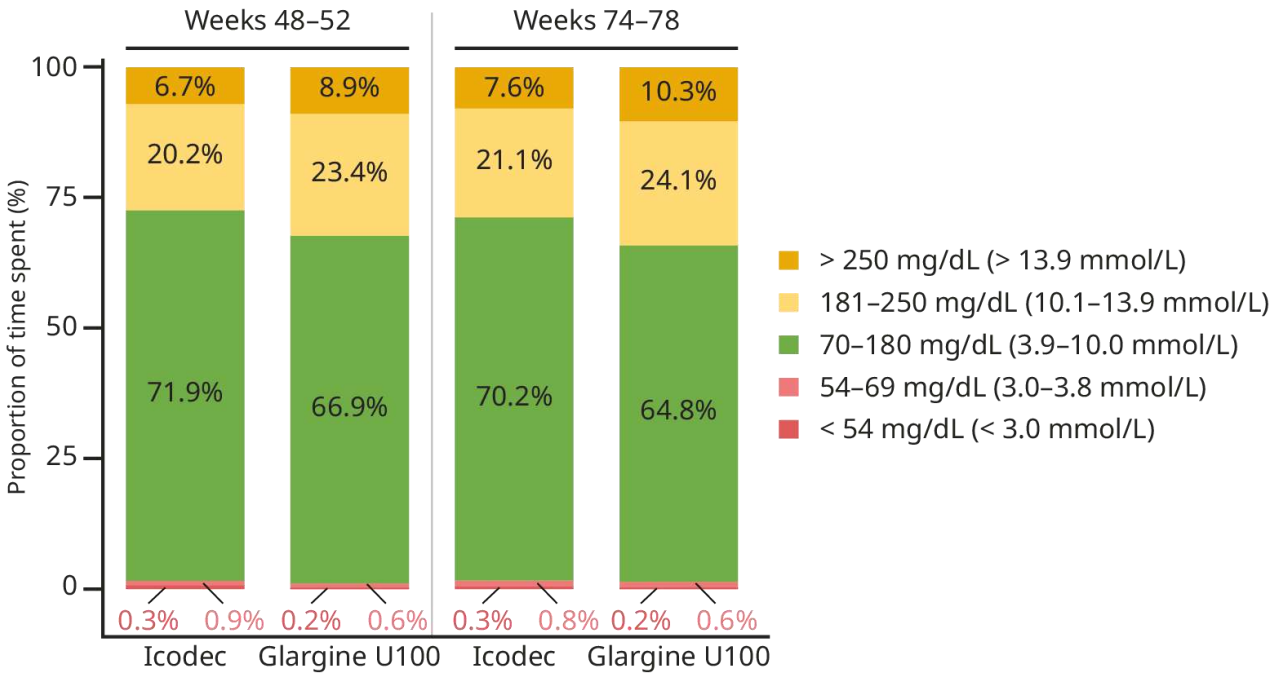
Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

Results

CGM: Percentage of time spent with glucose levels in range (70–180 mg/dL [3.9–10.0 mmol/L])

- During weeks 48–52, and during weeks 74–78, participants receiving icodec spent a significantly greater proportion of time in range than those receiving glargine U100 (ETD [95% CI]: 4.27 [1.92, 6.62] %-points), confirming superiority of icodec (P < 0.001)
  - This translates to approximately 1 hour and 1 minute of additional time spent in range per day with icodec compared with glargine U100
- On average, icodec, but not glargine U100, achieved the international recommended target for time in range of > 70% in both trial phases1,a

Figure 1B. Continuous glucose monitoring

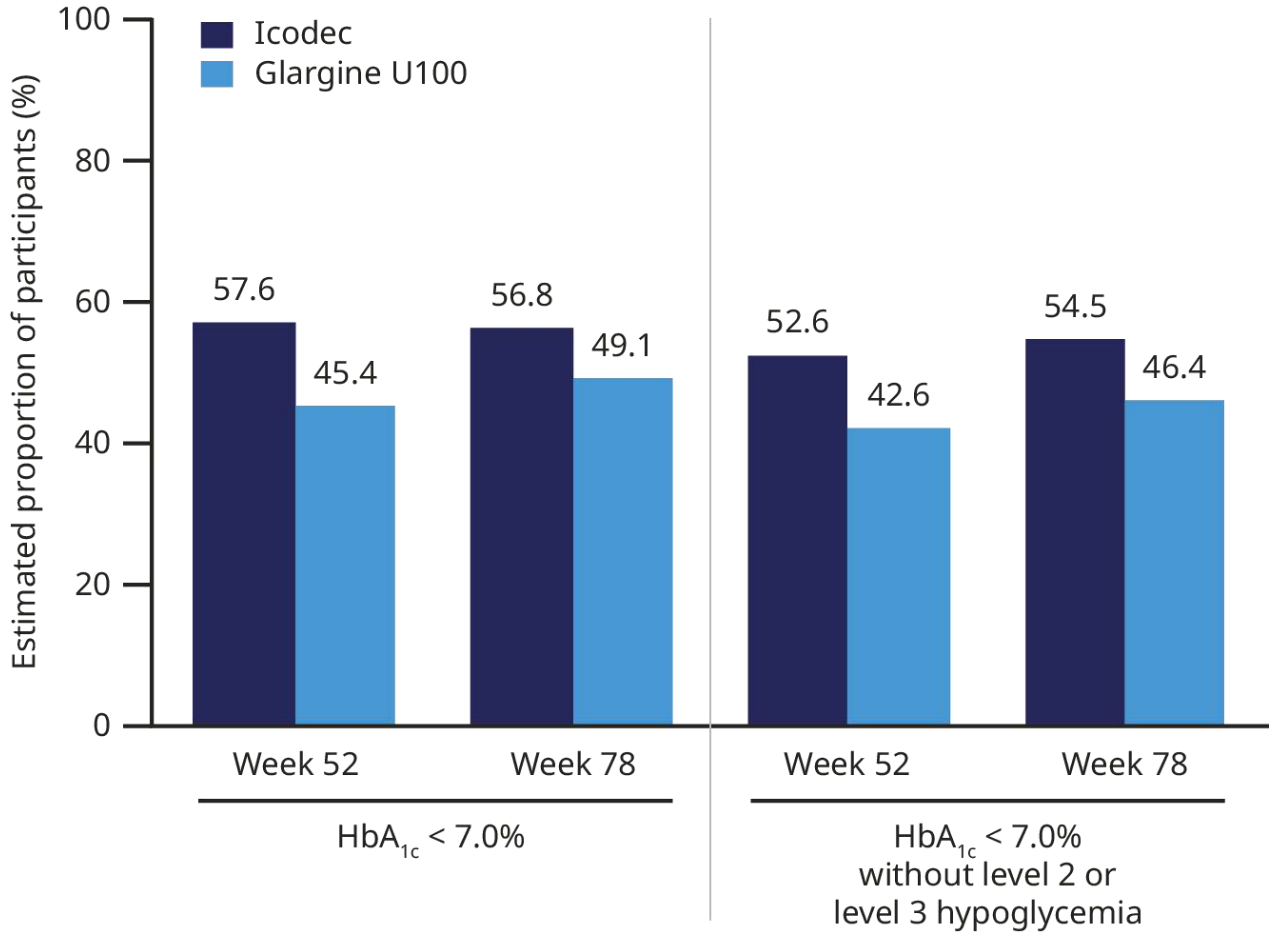


Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

Results

Proportion of participants achieving HbA_{1c} targets

- At both week 52 and week 78, a greater proportion of participants receiving icodec than of those receiving glargine U100 achieved:
- HbA1c < 7.0%
- HbA1c < 7.0% without clinically significant or severe hypoglycemia



Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

Results

Overall hypoglycemic episodes

- Hypoglycemia rates in both treatment arms were below one hypoglycemic event per PYE from baseline to week 52 and from baseline to week 83
- From baseline to week 83, 226 clinically significant[a] hypoglycemic events occurred in 61 participants (12.4%) receiving icodec compared with 114 events in 66 participants (13.4%) receiving glargine U100
- Over the trial duration, three participants (0.6%) receiving icodec experienced 105 of the 226 clinically significant[a] hypoglycemic events
- One episode of severe[b] hypoglycemia occurred with icodec, and seven episodes occurred with glargine U100

[a]Clinically significant (level 2) hypoglycemia: blood glucose < 54 mg/dL (< 3.0 mmol/L), confirmed by blood glucose meter. [b]Severe (level 3) hypoglycemia: hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery
Glargine U100, insulin glargine U100; icodec, insulin icodec; PYE, patient-year of exposure (1 PYE = 365.25 days)

Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

ONWARDS 3

Once-weekly insulin icodec vs once-daily insulin degludec in adults with insulin-naive type 2 diabetes: the ONWARDS 3 randomized clinical trial

Ildiko Lingvay, Marisse Asong, Cyrus Desouza, Pierre Gourdy, Soumitra Kar, André Vianna, Tina Vilsbøll, Siri Vinther, Yiming Mu

Published online in *JAMA* on 24 June 2023

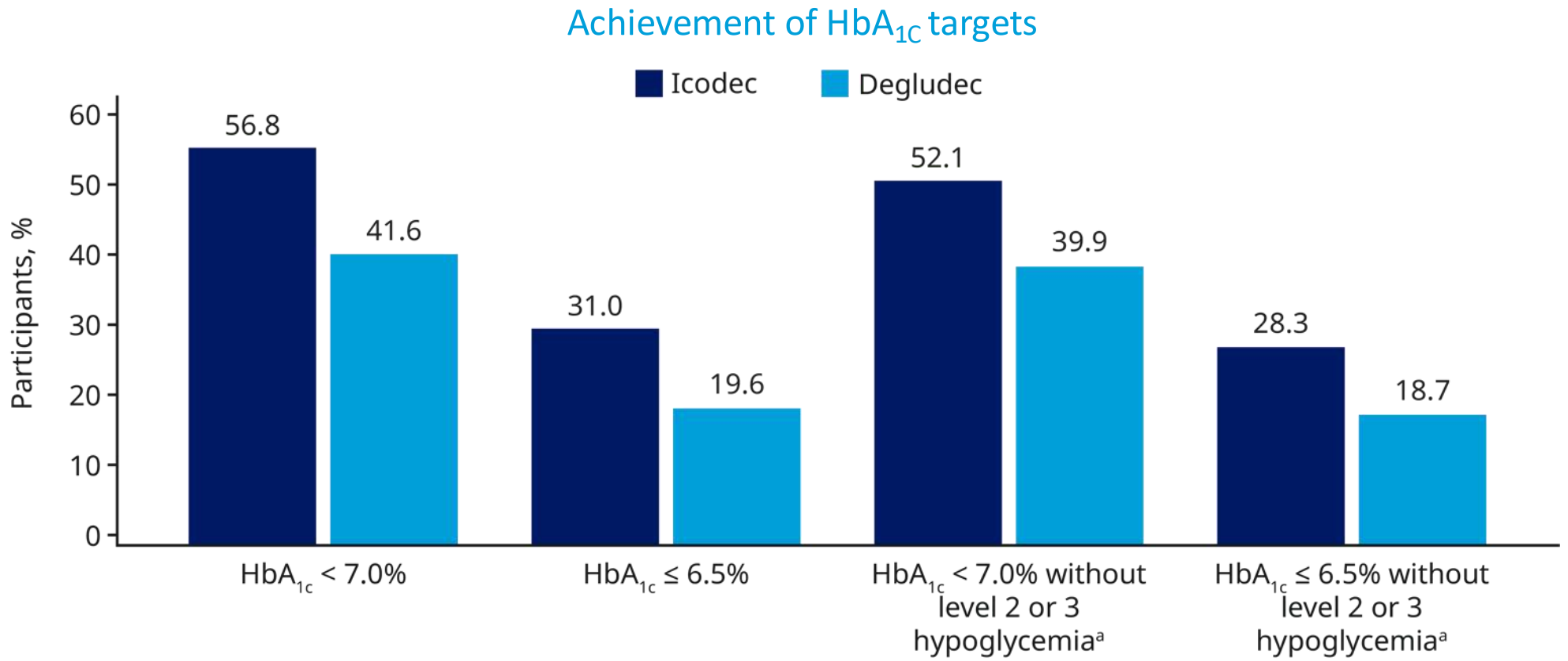
A randomized, **double-masked**, double-dummy, active-controlled, treat-to-target, phase 3a trial

Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

Once-weekly icodec (n = 294) Once-daily degludec (n = 294)

Results: - 1.6% with Icodec vs – 1.4% with Degludec

- Based on achievement of noninferiority ($p < 0.001$), superiority was tested and confirmed ($p = 0.002$)



Lingvay I *et al. JAMA* 2023; DOI: 10.1001/jama.2023.11313 (NCT04795531)

ONWARDS 5

Once-weekly insulin icodec with dosing guide app versus oncedaily basal insulin analogues in insulin-naive type 2 diabetes (ONWARDS 5)

Harpreet S. Bajaj, MD, MPH; Jens Aberle, MD; Melanie Davies, MBChB, MD; Anders Meller Donatsky, MD, PhD;

Marie Frederiksen, MSc; Dilek G. Yavuz, MD; Amoolya Gowda, MD; Ildiko Lingvay, MD, MPH, MSCS; and Bruce Bode, MD

Published on Annals of Internal Medicine doi:10.7326/M23-1288

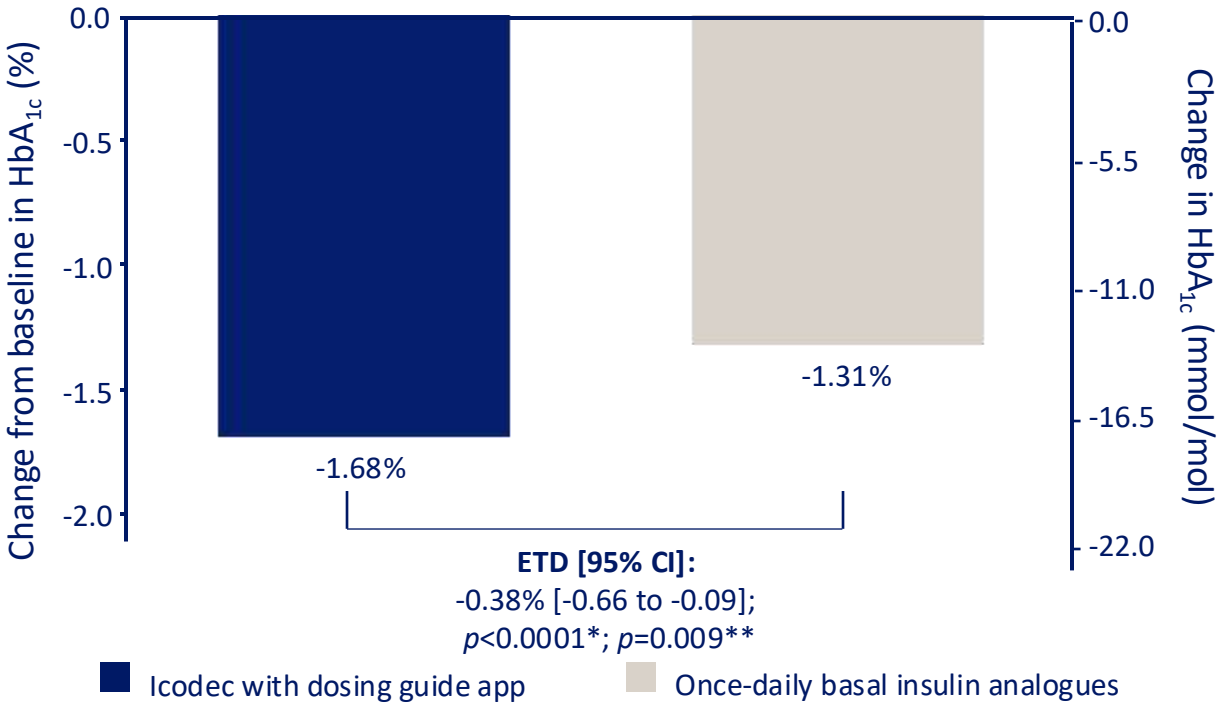
1085 individuals, RCT of 1 yr duration

Rosenstock J *et al. N Engl J Med* 2023; DOI: 10.1056/NEJMoa2303208

Change in HbA_{1c} and safety summary

Icodec in insulin-naïve T2D, in an RCT with real-world elements

Baseline HbA_{1c}: 8.9%



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

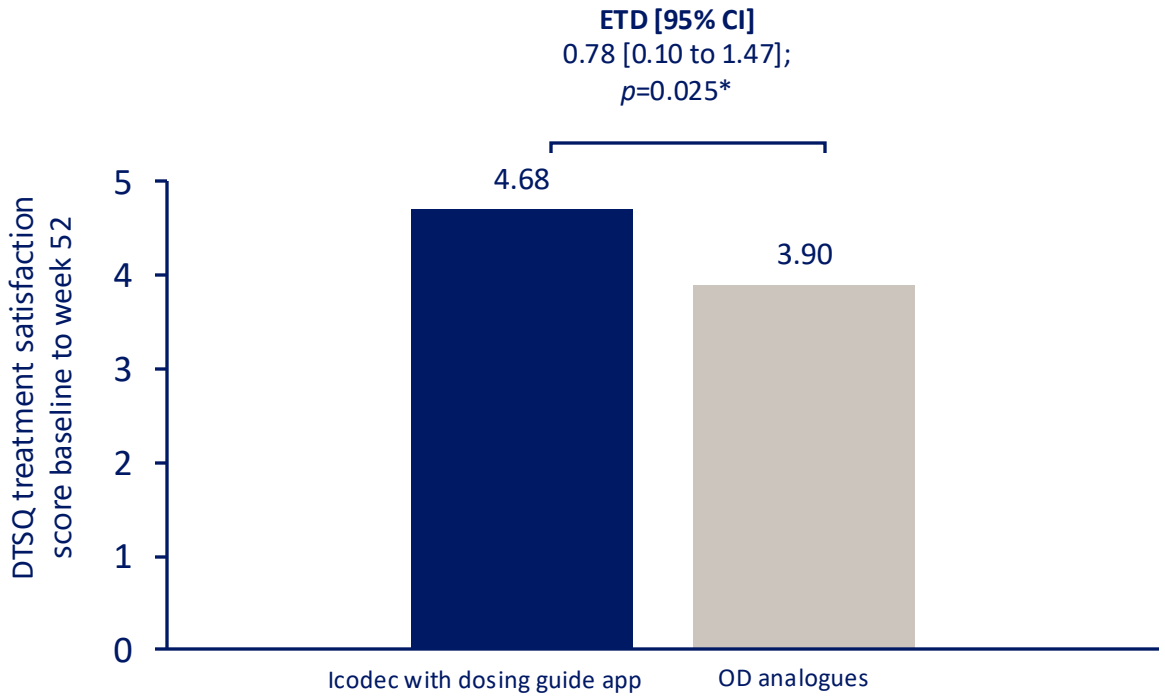
Icodec with dosing guide app	0.19
Once-daily basal insulin analogues*	0.14

No statistically significant difference in estimated rate of clinically significant or severe hypoglycaemia

The trial demonstrated non-inferiority and superiority in HbA_{1c} change from baseline to week 52 with insulin icodec with dosing guide app compared to once-daily basal insulin analogues

DTSQ treatment satisfaction score change from baseline to week 52

Icodec in insulin-naïve T2D, in an RCT with real-world elements



The treatment satisfaction score is calculated from six questions covering:

- Convenience
- Flexibility
- Satisfaction
- Willingness to recommend treatment

Statistically significantly higher change from baseline to week 52 **in total treatment satisfaction score with once-weekly icodec with dosing guide app** versus once-daily analogues

ONWARDS 4

Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 indivudals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, treat-to-target, non-inferiority trial

Chantal Mathieu, Björg Ásbjörnsdóttir, Harpreet S Bajaj, Wendy Lane, Ana Laura S A Matos, Sreenivasa Murthy, Karolina Stachlewska, Julio Rosenstock

Published online in *The Lancet* on 5 May 2023

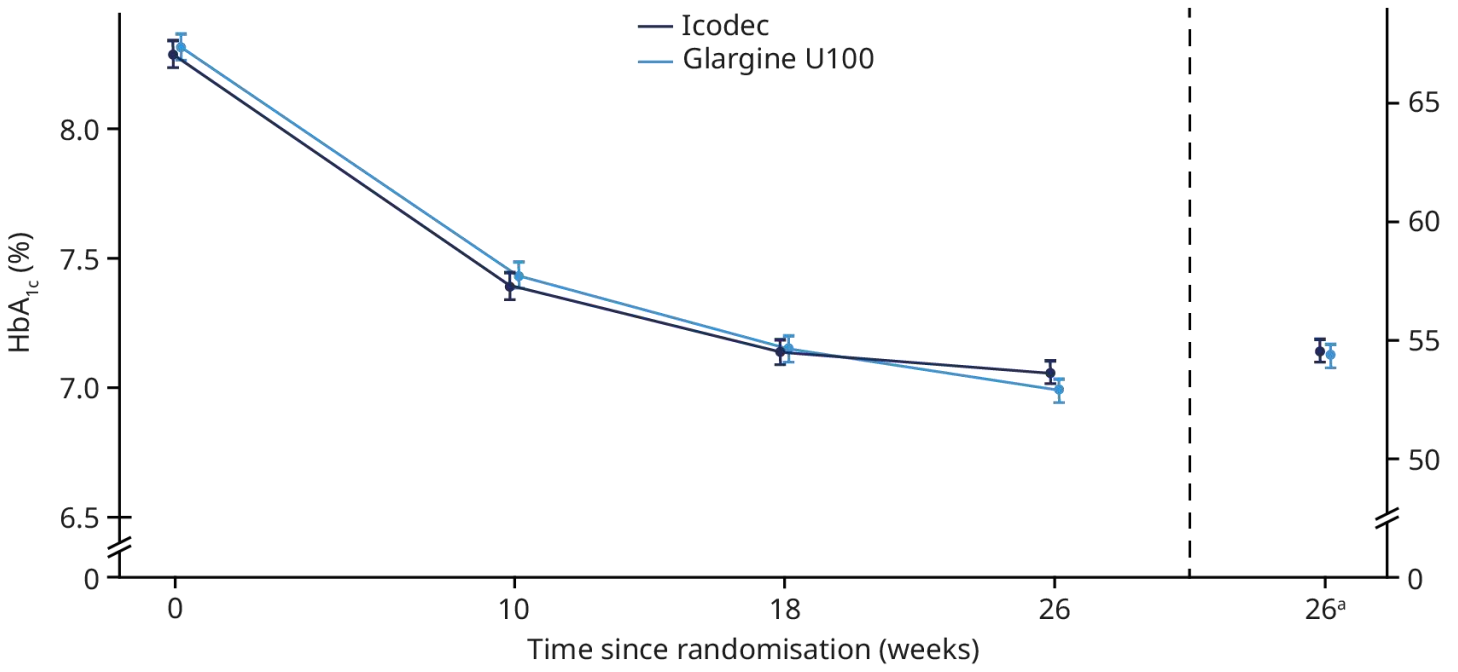
Trial number: NCT04880850

Lingvay I *et al. JAMA* 2023; DOI: 10.1001/jama.2023.11313 (NCT04795531)

Results

Change in HbA_{1c} from baseline to week 26 (primary endpoint)

Figure 2A. Mean glycated haemoglobin over time



Icodec (n = 291)	Glargine U100 (n = 291)

- Estimated mean change in HbA_{1c} from baseline to week 26 was −1.16%-points for icodec and −1.18%-points for glargine U100, with an ETD of 0.02%-points (95% CI −0.11–0.15)
- Non-inferiority of icodec versus glargine U100 was confirmed ($p < 0.0001$)

Lingvay I *et al. JAMA* 2023; DOI: 10.1001/jama.2023.11313 (NCT04795531)

Making sense of the available studies

- Once weekly insulin Icodec is effective.
- It can reduce HbA1c to a similar, **if not to a greater extent**, compared with daily analogues.
- It is safe.
- There were no signs of specific reactions to the drugs in terms of injection site reactions, systemic reactions, tumorigenesis, excessive weight gain or production of antibodies against the molecules.
- Icodec is a promising tool in the diabetologist's armamentarium for diabetes treatment.

Lingvay I *et al. JAMA* 2023; DOI: 10.1001/jama.2023.11313 (NCT04795531)

Once-weekly basal insulin icodec: Looking ONWARDS from pharmacology to clinical trials

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 16 (2022)

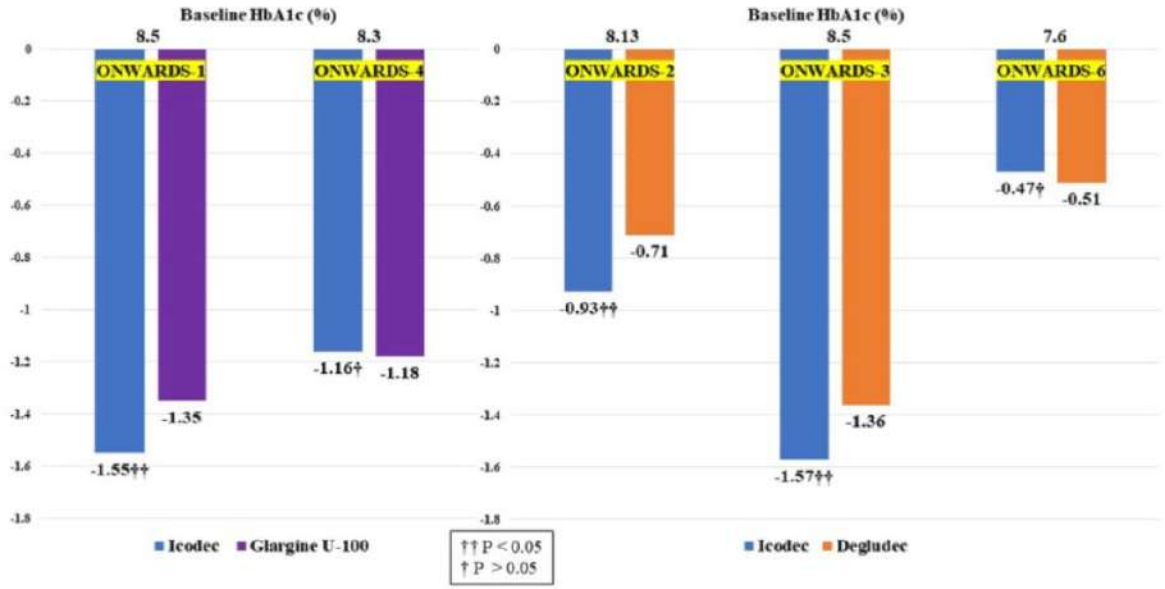


Fig. 2. HbA1c lowering with once-weekly insulin icodec vs. once-daily insulin glargine (U-100) or degludec.

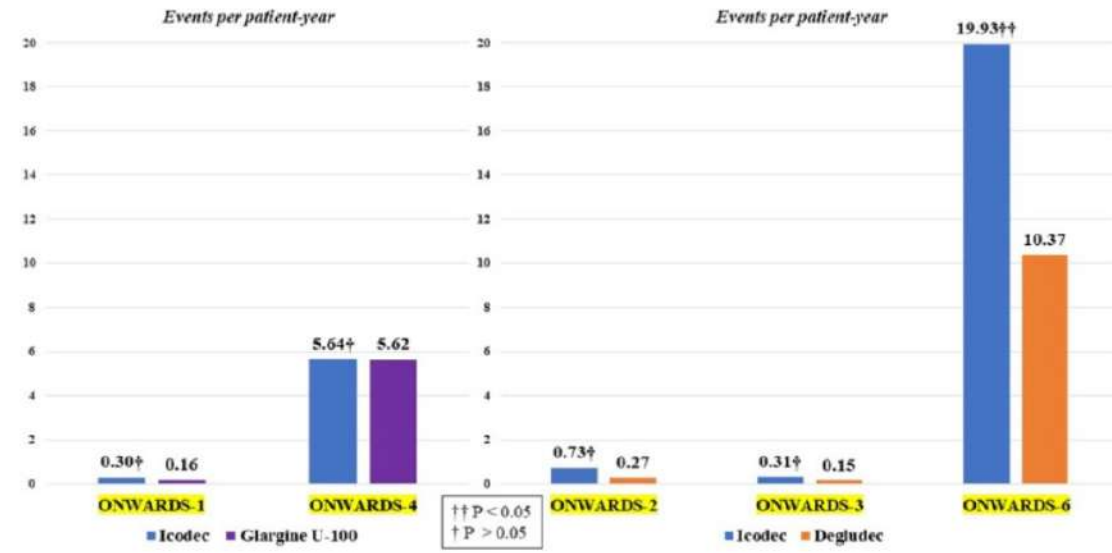


Fig. 3. Rate of level 2 or 3 hypoglycemia with once-weekly insulin icodec vs. once-daily insulin glargine (U-100) or deglude

Results: Phase 1 study showed insulin icodec having a half-life of 196 h (>1 week) while a steady state is achieved after 3 to 4 weekly injections. Phase 2 studies compared once-weekly icodec to insulin glargine (U-100) and found a similar glucose control with no significantly greater hypoglycemia risks. Top-line results from the five phase 3 studies reported better glucose control with once-weekly icodec compared to both once-daily insulin glargine (ONWARDS 1) and once-daily degludec (in both ONWARDS 2 and 4) with similar rates of hypoglycemia in type 2 diabetes, although there was a higher hypoglycemic event with insulin icodec in type 1 diabetes (ONWARDS 6) compared to once-daily degludec despite a similar glycemic control.

Conclusion: A brighter prospect of once-weekly insulin icodec is on the card in particular in type 2 diabetes in terms of reducing injection pricks by >85% vs. once-daily basal insulin analogs, although few unknowns still exist.

BIF

Il collegamento dell'insulina alla regione cristallizzabile del **frammento (Fc) dell'immunoglobulina G (IgG)** estende l'emivita dell'insulina perché la proteina di fusione beneficia della stessa via di riciclo che conferisce un'emivita relativamente lunga alle IgG endogene

Diabetes Mellitus and Glucose Metabolism
DYSREGULATED METABOLIC RESPONSE

Preclinical Characterization of Once Weekly Basal Insulin Fc (BIF)

Julie S. Moyers, PhD, Ryan J. Hansen, PhD, Jonathan W. Day, PhD, Craig D. Dickinson, PhD, Chen Zhang, MS, Steven D. Kahl, BS, Xiaoping Ruan, MD, Liyun Ding, BS, Robin M. Brown, BS, Hana E. Baker, PhD, John M. Beals, PhD.
Eli Lilly and Company, Indianapolis, IN, USA.

Diabetes Mellitus and Glucose Metabolism
CLINICAL TRIALS IN DIABETES AND METABOLIC DISEASE

Basal Insulin Fc (BIF), A Novel Insulin Suited For Once Weekly Dosing For The Treatment of Patients With Diabetes Mellitus

Tim Heise, MD1, Jenny Chien, PhD2, John Beals, PhD2, Charles Benson, MD, PhD2, Oliver Klein, MD1, Julie S. Moyers, PhD2, Axel Haupt, MD2, Edward J. Pratt, MD2.
1Profil, Neuss, Germany, 2Eli Lilly and Company, Indianapolis, IN, USA.

L'insulina settimanale BIF, è un **agonista selettivo per il recettore dell'insulina** e fornisce un agonismo completo, sebbene abbia **un'affinità inferiore** (2 ordini di grandezza) per questo rispetto all'insulina umana.
È interiorizzato dal recettore dell'insulina in misura simile all'insulina umana, ma ha una **potenza alquanto ridotta.**

- **la concentrazione plasmatica massima dopo singola dose sottocutanea è stata raggiunta il giorno 4;**
- **un'emivita media di circa 17 giorni;**
- **l'attività ipoglicemizzante è stata mantenuta per ≥5 giorni**

il **rapporto picco : minimo settimanale allo stato stazionario del BIF una volta alla settimana era di circa 1,1** rispetto a un rapporto picco : minimo giornaliero di 1,8 per l'insulina glargine giornaliera: **profilo insulinico molto più piatto.**

Weekly Basal Insulin Fc (BIF)

Weekly basal insulin Fc (BIF Weekly basal insulin Fc) s designed for once-weekly subcutaneous administration. BIF is comprised of a human insulin receptor (IR) agonist fused to a human immunoglobulin G2 (IgG2) fragment crystallizable (Fc) domain. Similar to other Fc-conjugated molecules, it is expected that the presence of the Fc domain, in combination with controlled IR-mediated clearance because of reduced IR affinity, will lead to prolonged half-life

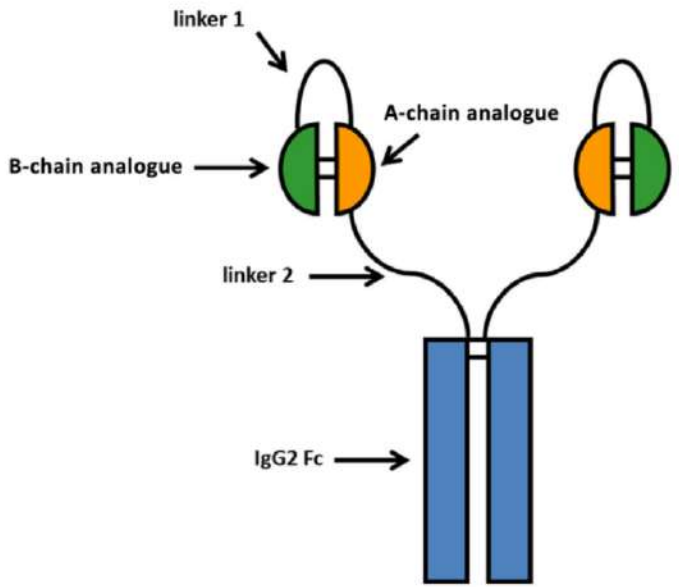


FIGURE 1 Schematic of weekly basal insulin Fc (BIF) structure.[22]
IgG2, immunoglobulin G2

Diabetes Obes Metab. 2023;:

Attributes

- Selective insulin receptor agonist
  - Selectivity versus IGF-1 receptor
  - Low mitogenicity potential
- Pharmacokinetic profile consistent with once weekly subcutaneous dosing
- Formulation compatible with single-use or multi-use devices
  - Can be co-formulated with weekly incretins
- Low immunogenicity risk

Once-Weekly Basal Insulin Fc Demonstrated Similar Glycemic Control to Once-Daily Insulin Degludec in Insulin-Naive Patients With Type 2 Diabetes: A Phase 2 Randomized Control Trial

Diabetes Care 2023;46:1060–1067 | https://doi.org/10.2337/dc22-2396

Once-weekly basal insulin Fc (BIF) demonstrated similar glycemic control to once-daily insulin degludec in insulin-naive patients with type 2 diabetes (T2D) in this phase 2 randomized controlled trial. CGM, continous glucose monitoring.

Background

Once-weekly BIF combines a novel single-chain insulin variant with a human IgG_2 Fc domain and is designed for once-weekly subcutaneous administration for the treatment of diabetes.

Patient Population

N = 278 insulin-naive people with T2D

55% male 45% female

Mean Baseline Characteristics:

Age = 58 years

Duration of T2D = 10 years

HbA_{1c} = 8.0%

Study Design

2-week screening/lead-in

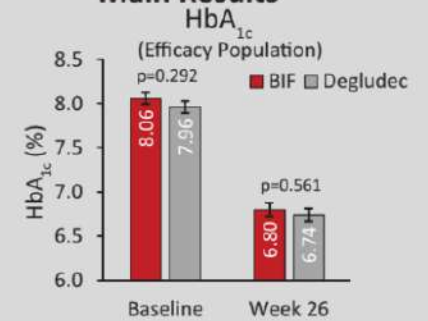
↓

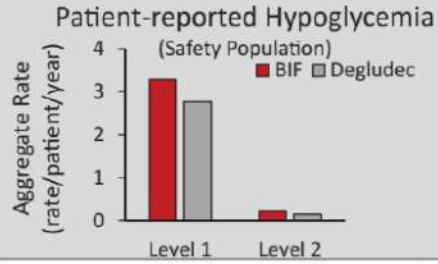
26-week treatment period

BIF administered once weekly ↔ Degludec -administered once daily

- Treat-to-target fasting glucose: BIF used 101-140 mg/dL (5.6 to <7.8 mmol/L) for the first 2 weeks only; 80-100 mg/dL (4.4 to <5.6 mmol/L) was used for both treatments
- All patients underwent intermittent blinded CGM (Abbott Libre Pro)
- Assessed HbA_{1c}, fasting glucose, incidence and rate of hypoglycemia

Main Results





Conclusion

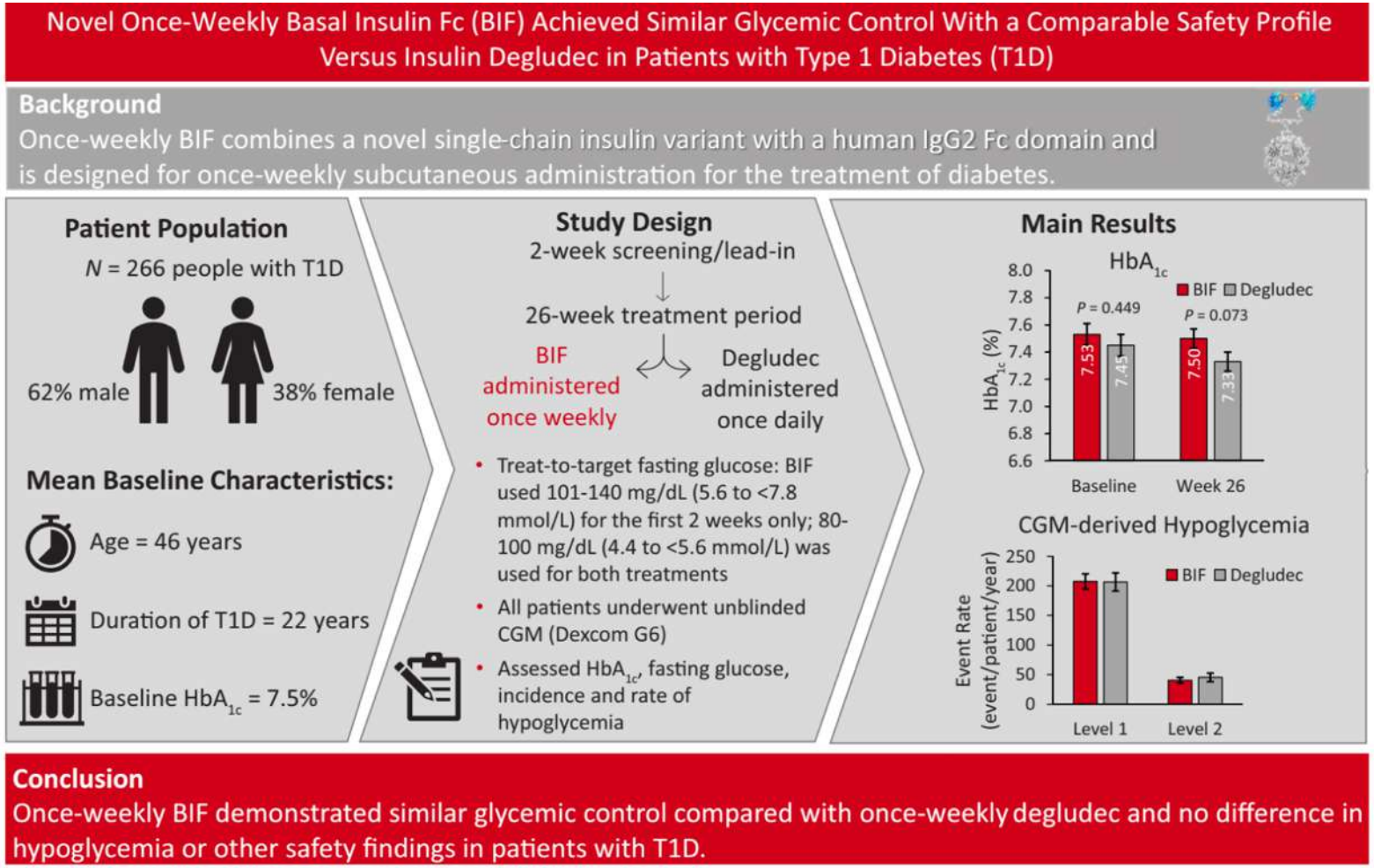
Once-weekly BIF demonstrated excellent glycemic control similar to Once-daily degludec and no difference in hypoglycemia or other safety findings in insulin-naive patients with T2D.

ARTICLE HIGHLIGHTS

- This study assessed once-weekly basal insulin Fc (BIF) as a treatment option for insulin-naive patients with type 2 diabetes (T2D).
- The research question was whether BIF is a safe and efficacious treatment for insulin-naive patients with T2D.
- BIF administered once weekly achieved similar glycemic control with similar hypoglycemia risk compared with once-daily degludec.
- BIF has the potential to safely and effectively manage glycemic control in insulin-naive patients with T2D while reducing injection burden.

Novel Once-Weekly Basal Insulin Fc Achieved Similar Glycemic Control With a Safety Profile Comparable to Insulin Degludec in Patients With Type 1 Diabetes

Diabetes Care 2023;46:1052–1059 | https://doi.org/10.2337/dc22-2395



ARTICLE HIGHLIGHTS

- Once-weekly basal insulin Fc (BIF) was administered as treatment for patients with type 1 diabetes (T1D).
- We wanted to determine if BIF is safe and efficacious for patients with T1D.
- BIF demonstrated similar glycemic control to daily insulin degludec, without increasing the risk of hypoglycemia in patients with T1D.
- BIF has the potential to safely and effectively provide glycemic control while reducing the injection burden in T1D.

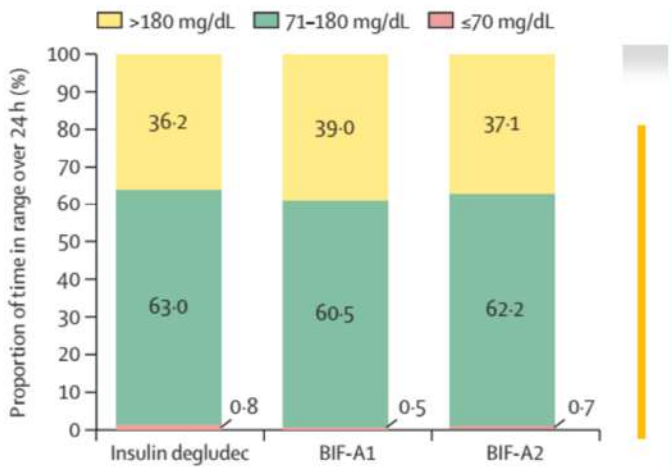
Diabetes Care 2023;46(5):1052–1059

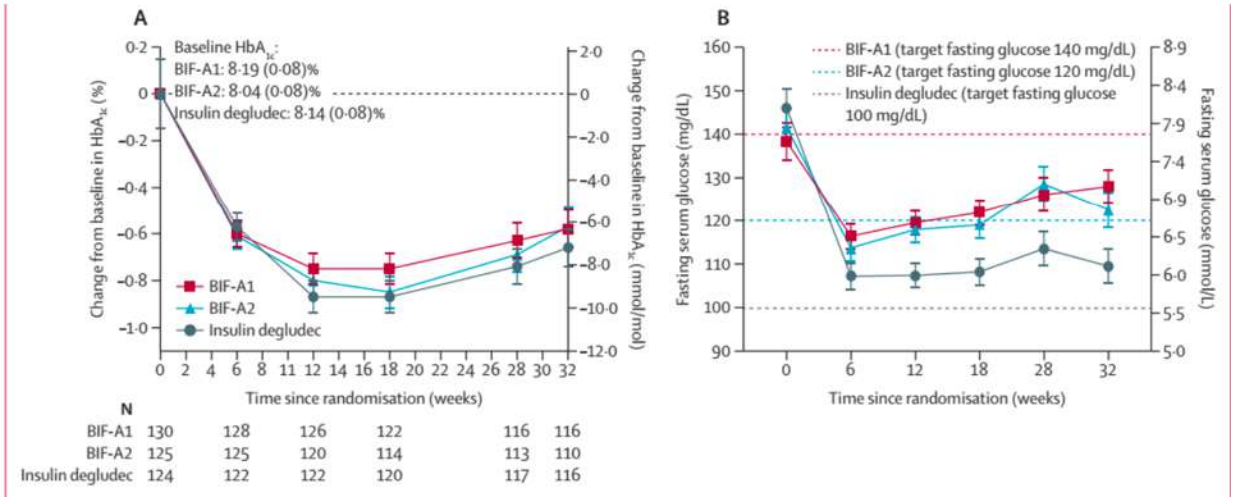
Safety and efficacy of once-weekly basal insulin Fc in people with type 2 diabetes previously treated with basal insulin: a multicentre, open-label, randomised, phase 2 study

Lancet Diabetes Endocrinol
2023; 11: 158–68

Implications of all the available evidence
Weekly BIF treatment resulted in stable glycaemic control in people with type 2 diabetes previously treated with basal insulin. The reduced treatment burden of once-weekly insulin compared with daily insulin has the potential to improve treatment adherence and positively affect glycaemic outcomes. These BIF data show promise for patients who require insulin treatment intensification. These findings support continued development of BIF as a once-weekly insulin treatment of diabetes.

Interpretation Weekly BIF achieved a similar efficacy compared with degludec despite higher fasting glucose targets in the BIF groups. Higher fasting glucose targets and lower glucose variability might have contributed to lower hypoglycaemia rates for BIF compared with degludec. These findings support continued development of BIF as a once-weekly insulin treatment for people with diabetes.





Diabetes Mellitus and Glucose Metabolism
IMPROVING DIABETES CARE: HOSPITAL DISCHARGE, COMPLICATIONS, AND NOVEL INSULIN THERAPY

Once Weekly Basal Insulin Fc (BIF) is Safe and Efficacious in Patients with Type 2 Diabetes Mellitus (T2DM) Previously Treated With Basal Insulin

Juan Pablo Frias, MD1, Jenny Chien, PhD2, Qianyi Zhang, PhD2, Emmanuel Chigutsa, PhD2, William Landschulz, MD, PhD2, Paula Wullenweber, BS2, Axel Haupt, MD2, Christof Kazda, MD, PhD, MscPM2.
1National Research Institute, San Diego, CA, USA, 2Eli Lilly and Company, Indianapolis, IN, USA.

The study design included **2 different dosing algorithms** fo BIF (BIF-A1 and BIF-A2) with two different fasting glucose **(FG) targets of ≤140 mg/dL (BIF-A1) and ≤120 mg/dL (BIF-A2). Insulin degludec was titrated to a FG target o ≤100mg/ dL**

In summary, BIF, when administered weekly according to either dosing algorithm, **was noninferior** to insulin degludec for glycemic control as measured by change in HbA1c after 32 weeks **with a lower rate** of documented and nocturnal hypoglycemia ≤70 mg/dL and less weight gain.

Table 2
Summary of phase 2 clinical data for BIF in patients with T2D who were previously treated with basal insulin and up to three oral antidiabetic medications for 32 weeks (NCT03736785) [73,74].

Outcome	BIF-A1 ($n = 135$) FPG target of 140 mg/dL	BIF-A2 ($n = 132$) FPG target of 120 mg/dL	Insulin degludec (n = 132) FPG target of 100 mg/dL
Mean baseline $HbA_{1c} \pm SD$, %	8.20 ± 0.87	8.03 ± 0.89	8.13 ± 0.88
Change in HbA_{1c}, LS mean ± SE, %	−0.58 ± 0.083 (noninferior to insulin degludec)	−0.57 ± 0.085 (noninferior to insulin degludec)	−0.66 ± 0.084
Change in FPG, LS mean ± SE, mg/dL	−13.1 ± 4.01	−18.6 ± 4.14	−31.5 ± 4.03
Hypoglycemic events (<54 mg/dL [<3.0 mmol/L]),[a] mean ± SE, *n* events/patient/year	0.73 ± 0.12 (not significant vs. degludec)	1.22 ± 0.38 (not significant vs. degludec)	1.56 ± 0.38
Change in body weight, LS mean ± SE, kg	1.0 ± 0.33 (significant vs. degludec)	1.0 ± 0.33 (significant vs. degludec)	2.0 ± 0.33
Nonserious AEs, n patients (%)[b]	17 (12.6)	29 (22.0)	13 (9.9)
Serious AEs, n patients (%)[b]	7 (5.2)	8 (6.1)	10 (7.6)
Serious hypoglycemic AEs, *n* events[c]	0	2	0

AE: adverse event. BIF: basal insulin fragment crystallizable. CI: confidence interval. FPG: fasting plasma glucose. HbA_{1c}: glycated hemoglobin. LS: least-squares. SD: standard deviation. SE: standard error. T2D: type 2 diabetes.
An inclusion criterion was the use of up to three oral antidiabetic medications, including dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, biguanides, alpha-glucosidase inhibitors, or sulfonylureas.
[a] Patients in the BIF-A1 and BIF-A2 treatment arms had significantly fewer hypoglycemic events than those in the insulin degludec treatment arm for all documented events of plasma glucose ≤70 mg/dL (≤3.9 mmol/L).
[b] Time frame up to 37 weeks.
[c] Patient-reported events of blood glucose of <54 mg/dL (<3.0 mmol/L).

Sono in corso due studi per confrontare BIF con insulina degludec in pazienti **mai trattati con insulina con T2D** (NCT04450394)
e in pazienti con T1D (NCT04450407).

Le persone con **T2D** **con controllo glicemico inadeguato** indicazione non è diversa da quella attualmente adottata per l'insulina basale una volta al giorno.

- **ridurre l'inerzia clinica aumentando così l'aderenza del pz al trattamento e la qualità della vita**
- pazienti che **necessitano di assistenza con le iniezioni**. (una anziché sette iniezioni a settimana)
- **un'intensificazione di terapia** es con GLP-1 RA una volta alla settimana, l'assunzione di un'insulina basale con la stessa frequenza di iniezione semplificherebbe la gestione.

T1D

- **minor numero di iniezioni**
- migliorare l'aderenza e il controllo della glicemia nei pazienti che possono saltare le dosi, in particolare **gli adolescenti.**
- avere un livello di insulina relativamente costante potrebbe **ridurre la frequenza della chetoacidosi diabetica** ,