Le nuove insuline ultrarapide e basali

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Dichiarazione sul Conflitto di Interessi

Io sottoscritto Pintaudi Basilio

dichiaro

di aver intrattenuto, negli ultimi due anni, interessi commerciali con le seguenti Aziende operanti nel campo sanitario:

Novo Nordisk

Eli Lilly

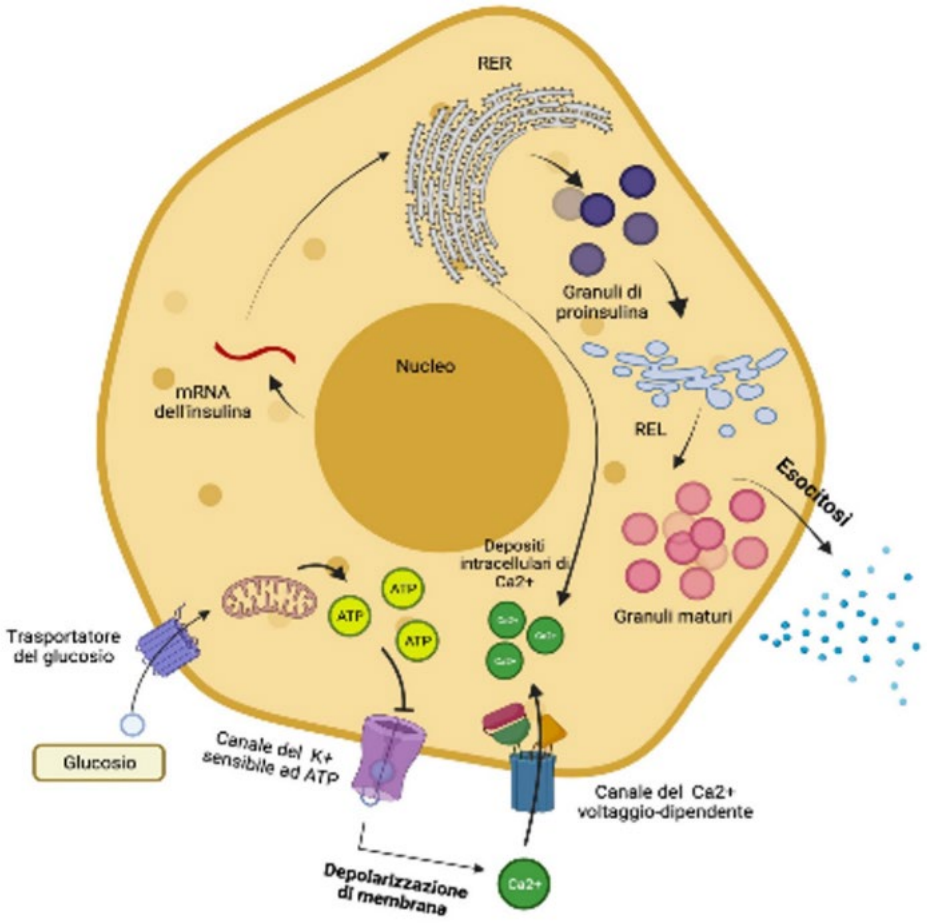
MSD

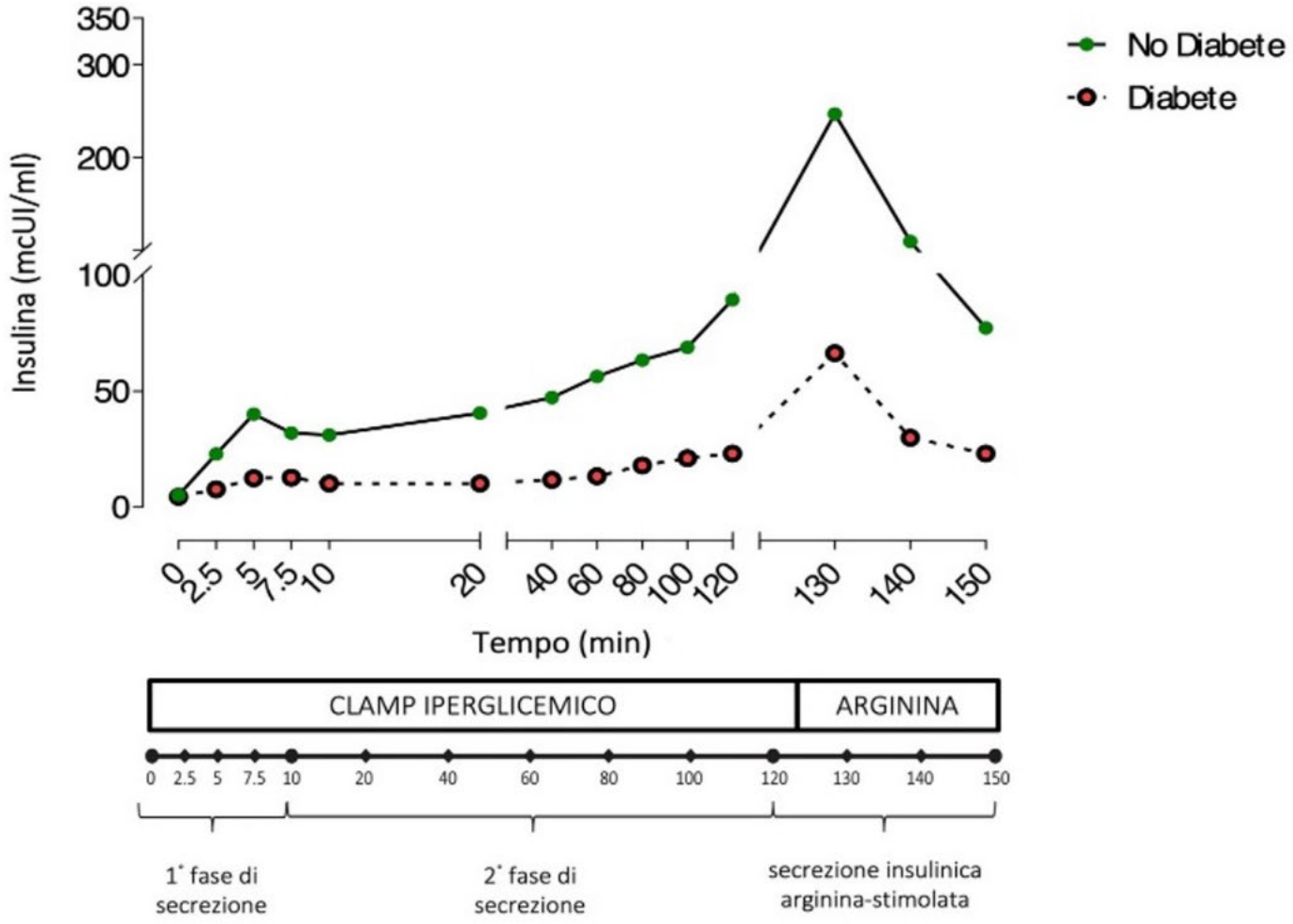
Theras

Pikdare

Sanofi

Una straordinaria fisiologia





triggering pathway

amplifying pathway

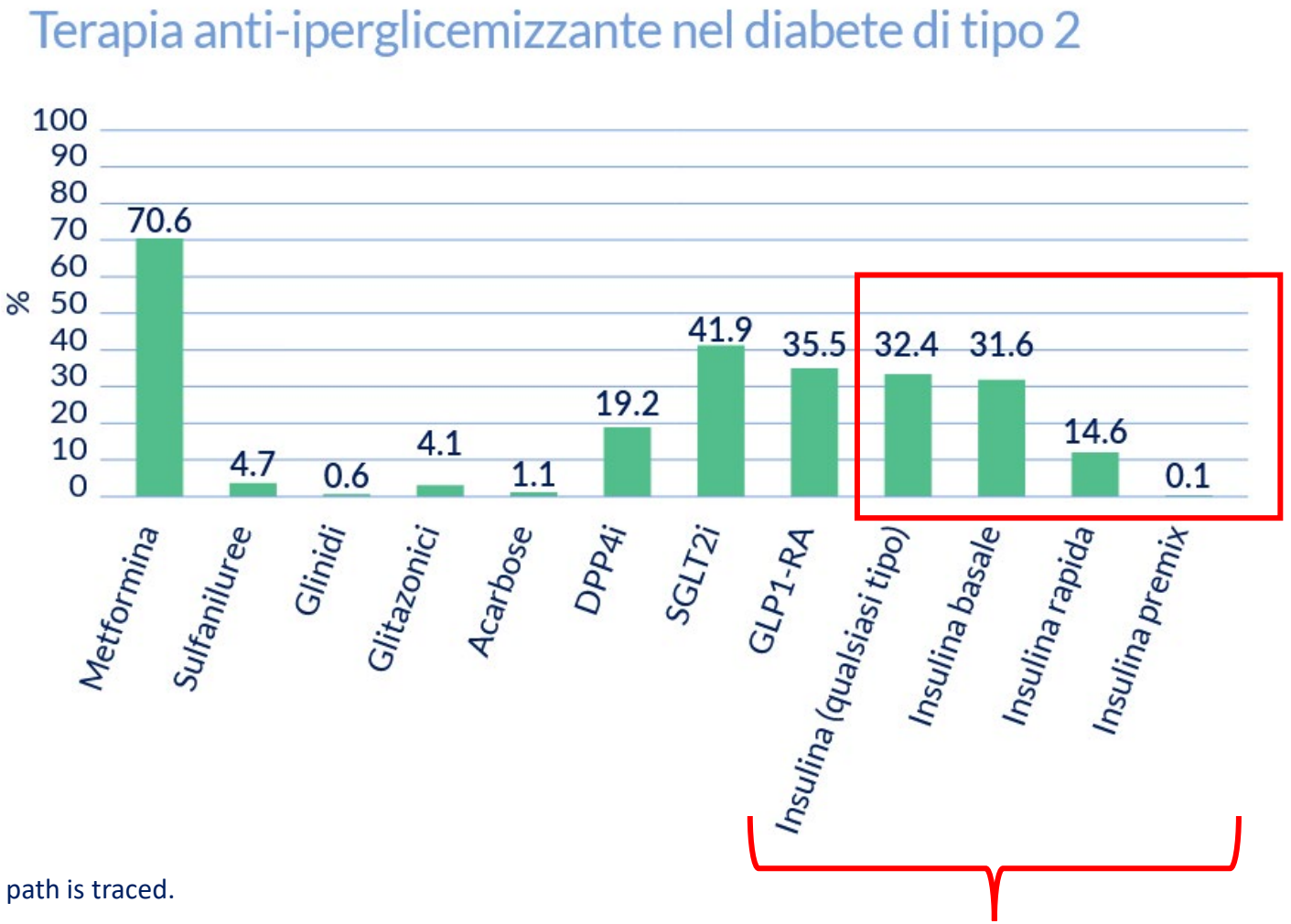
- piruvato (aumento del rapporto NADPH/NADP+ citosolici)
- prodotti del ciclo dei pentoso-fosfati
- GTP di origine mitocondriale
- FFAs

Di Giuseppe G et al. Il Diabete 2022;34:1

La terapia insulinica in Italia: suggestioni epidemiologiche

Persone con diabete coinvolte

- 48.041 **Diabete tipo 1** (+12.9%)*
- 680.122 **Diabete tipo 2** (+18.7%)*
- 13.785 **Diabete in gravidanza** (+8.5%)*



Type 2 diabetes specialist care in Italy in the AMD Annals initiative 2024: The path is traced. Diabetes Res Clin Pract 2025;225:112273.

Le ‘nuove’ insuline ultrarapide

PERSPECTIVES IN CLINICAL DIABETES

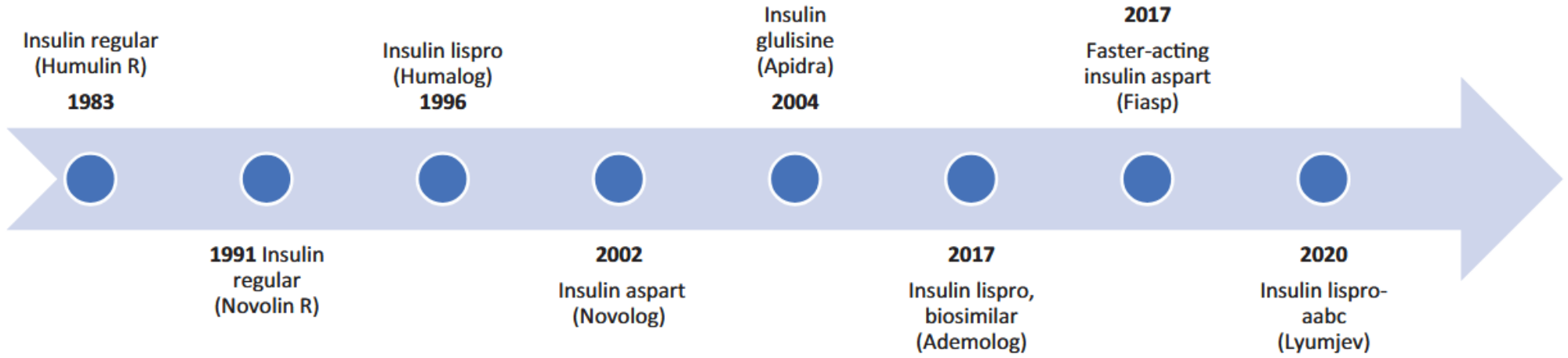


FIGURE 1 Timeline of U.S. Food and Drug Administration approval of bolus insulins (6).

Wong EY, Kroon L. Clin Diabetes 2021;39:415-423.

Premeal Injection of Rapid-Acting Insulin Reduces Postprandial Glycemic Excursions in Type 1 Diabetes

(▲) 30 min before the meal

(■) 15 min before the meal

(●) directly at the start of the meal

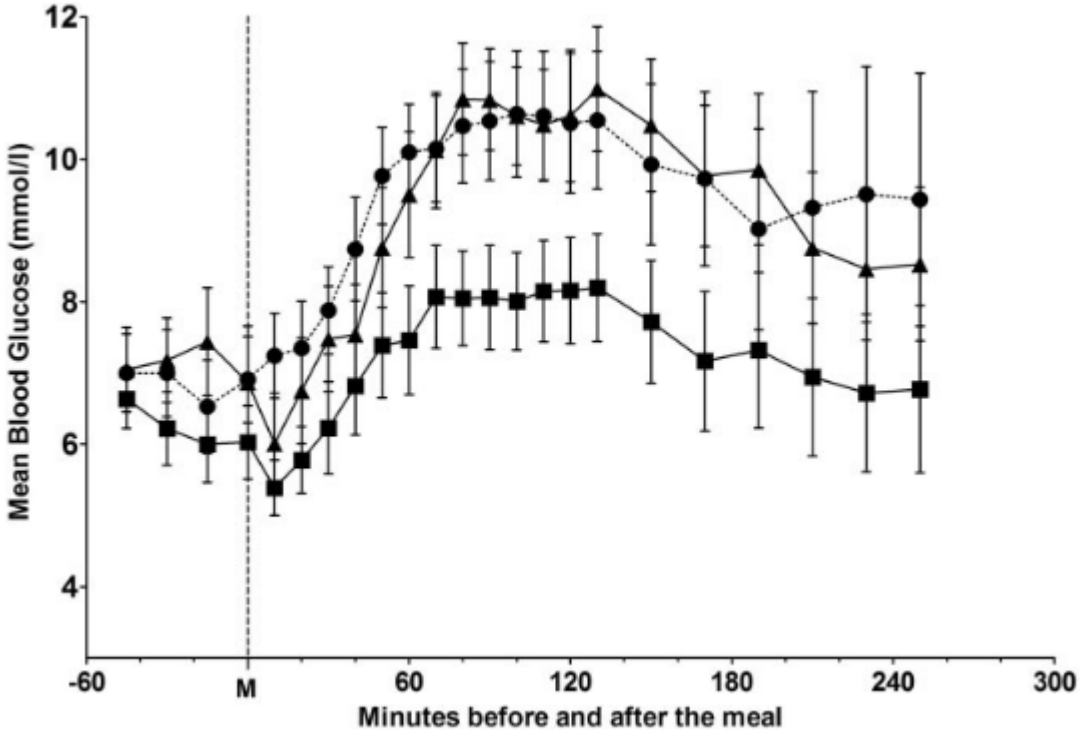
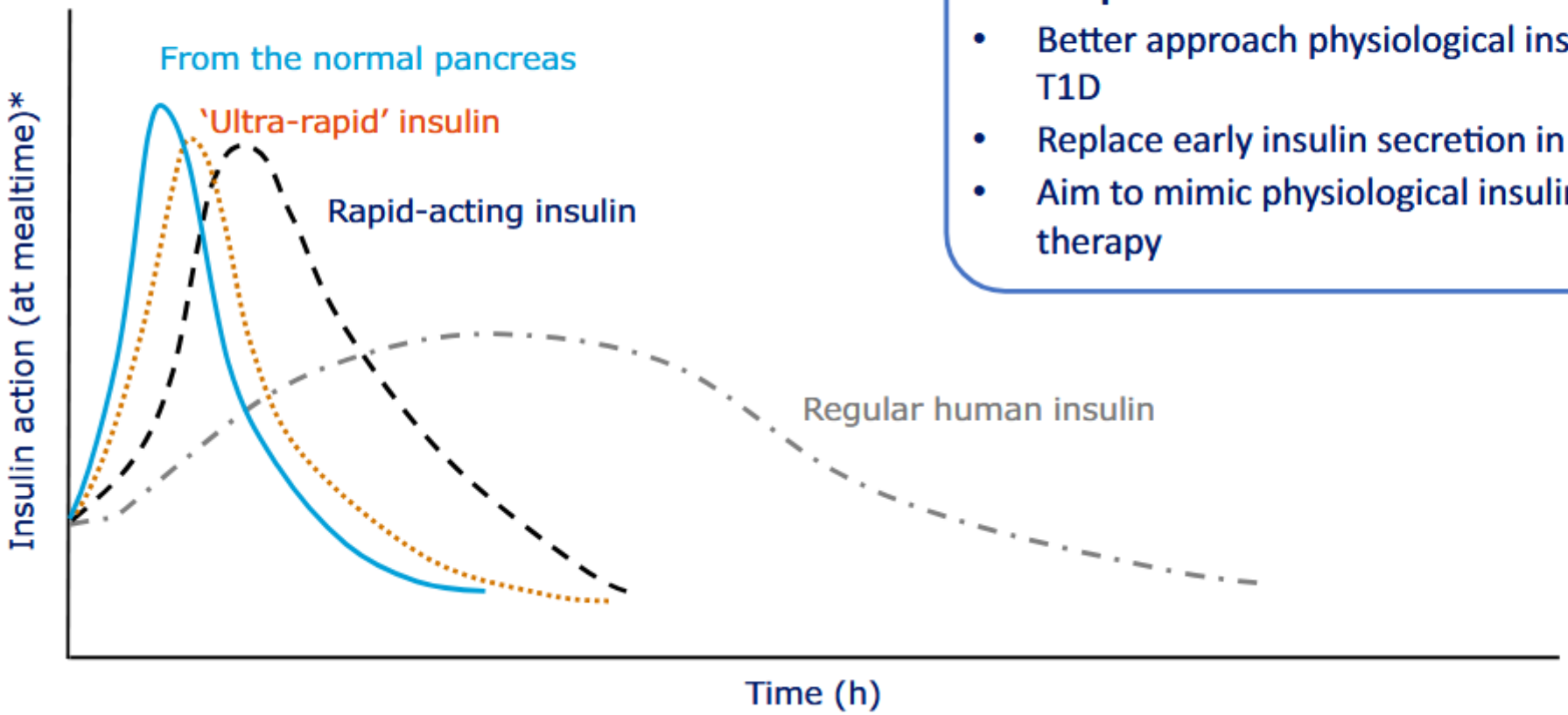


Table 1—*Summary of results for blood glucose and CGM data*

	Treatment arm −30	Treatment arm −15	Treatment arm 0	Overall *P* value (repeated-measures ANOVA)*
Blood glucose–derived outcomes				
AUC (mmol/l/min)	1.89 ± 0.72	0.41 ± 0.51	2.11 ± 0.66	0.043†
Maximum glucose excursion (mmol/l)	6.48 ± 0.76	4.77 ± 0.52	6.93 ± 0.76	0.038†
Peak glucose level (mmol/l)	11.74 ± 0.80	9.26 ± 0.72	12.29 ± 0.93	0.003†
Time spent in euglycemia (min)‡	182.5 ± 28.2	224.5 ± 25.0	90.5 ± 23.2	0.000†
Hypoglycemic events (no. of measurements)§	6 of 220	7 of 220	4 of 220	0.901
CGM–derived outcomes				
AUC (mmol/l/min)	2.32 ± 0.59	1.10 ± 0.11	1.89 ± 0.34	0.088
Maximum glucose (mmol/l)	11.48 ± 1.08	10.11 ± 0.59	11.31 ± 0.82	0.174
Maximum glucose excursion (mmol/l)	5.24 ± 1.01	4.37 ± 0.64	5.41 ± 0.67	0.537

Luijf YM et al. Diabetes Care 2010;33:2152-2155

Ultra-rapid insulin: approaching a physiological insulin profile even further

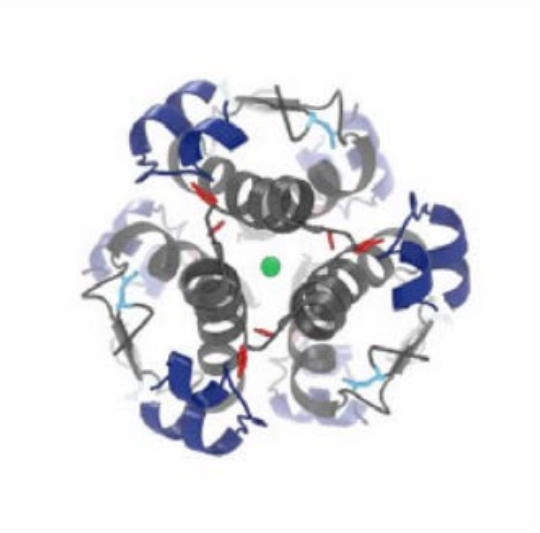


Ultra-rapid insulin should:

- Better approach physiological insulin secretion in T1D
- Replace early insulin secretion in T2D
- Aim to mimic physiological insulin profile for pump therapy

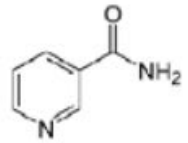
Evans M et al. Diabetes Ther 2019;10:1793-1800

Faster aspart insulin: la struttura molecolare



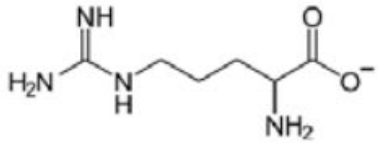
Insulin aspart

Niacinamide: absorption modifier



Vitamin B3

L-Arginine: added for stability



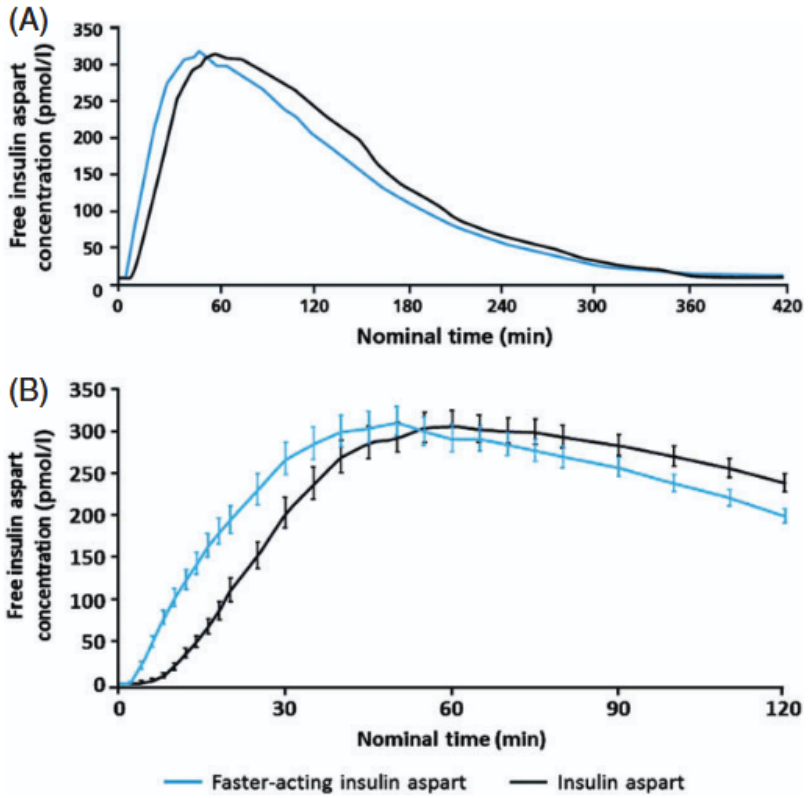
Naturally occurring amino acid

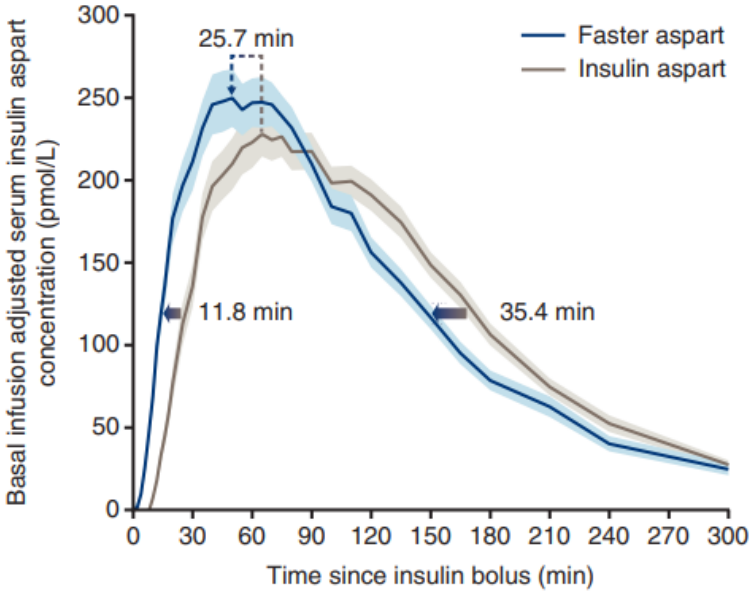
La niacinamide aumenta il flusso sanguigno sottocutaneo, migliorando così l'assorbimento dell'insulina, e riduce l'autoaggregazione dell'aspart.

Evans M et al. Diabetes Ther 2019;10:1793-1800

Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart

T. Heise[1], U. Hövelmann[1], L. Brøndsted[2], C. L. Adrian[2], L. Nosek[1] & H. Haahr[2]





Heise T et al. DOM 2017;19:208-215

	Faster-acting insulin aspart (N = 51) LS mean (CV or s.e.m.*)	Insulin aspart (N = 51) LS mean (CV or s.e.m.*)	Treatment ratio (95% CI) faster-acting insulin aspart/insulin aspart
Onset of glucose-lowering effect, min			
$t50\%GIR_{max}$	38.3 (2.22)*	46.1 (2.22)*	0.83 (0.73; 0.94)
$tGIR_{max}$	124.3 (5.87)*	135.2 (5.87)*	0.92 (0.84; 1.01)
Early glucose-lowering effect, mg/kg			
$AUC_{GIR,0-30\,min}$	56.2 (4.88)*	38.0 (4.88)*	1.48 (1.13; 2.02)
$AUC_{GIR,0-1\,h}$	183.7 (0.07)	140.2 (0.07)	1.31 (1.18; 1.46)
$AUC_{GIR,0-1.5\,h}$	360.4 (0.07)	308.3 (0.07)	1.17 (1.05; 1.30)
$AUC_{GIR,0-2\,h}$	554.5 (0.07)	502.2 (0.07)	1.10 (1.00; 1.22)
Overall glucose-lowering effect			
$AUC_{GIR,0-12\,h}$, mg/kg	1375.2 (0.06)	1404.7 (0.06)	0.98 (0.87; 1.11)
GIR_{max}, mg/(kg × min)	7.2 (0.05)	7.1 (0.05)	1.02 (0.93; 1.12)

Heise T et al. DOM 2015;17: 682-688

Faster Aspart: gli studi ONSET

ONSET 1 [45]		
Popolazione in Studio	**Disegno dello Studio**	**Risultati Principali**
Pazienti con diabete di tipo 1 in trattamento basal bolus e $HbA1_c$ 7-9%.	Studio doppio cieco, 3 braccia di trattamento di cui 1 open label (post-meal): 1. Faster Aspart (meal-time)+Detemir 2. Faster Aspart (post-meal)+Detemir 3. Aspart (meal-time)+Detemir Durata dello studio 52 settimane, 26 settimane con i 3 bracci + 26 settimane senza il braccio di trattamento Faster Aspart (post-meal)+Detemir	- Faster Aspart meal-time o post-meal non è inferiore rispetto ad Aspart nel ridurre la $HbA1_c$; - Faster Aspart meal-time si associa ad una maggiore riduzione della $HbA1_c$ rispetto a Aspart; - Faster Aspart si associa ad una maggiore riduzione della glicemia postprandiale dopo 1 e 2 ore rispetto alla Aspart al meal test; - La significativa riduzione della $HbA1_c$, ottenuta con Faster Aspart rispetto ad Aspart, è mantenuta durante tutta la durata dello studio - Profilo di sicurezza sovrapponibile (numero totale di ipoglicemie).
ONSET 2 [48]		
Pazienti con diabete di tipo 2 in trattamento con insulina basale, metformina±altri ipoglicemizzanti orali e $HbA1_c$ 7-9,5%.	Studio doppio cieco, 2 braccia di trattamento: 1. Faster Aspart (meal-time)+Glargine+Metformina 2. Aspart (meal-time)+Glargine+Metformina Durata dello studio 26 settimane.	- Faster Aspart meal-time non è inferiore rispetto ad Aspart nel ridurre la $HbA1_c$; - Faster Aspart si associa ad una maggiore riduzione della glicemia postprandiale dopo 1 ora rispetto alla Aspart al meal test; - Profilo di sicurezza sovrapponibile (numero totale di ipoglicemie).
ONSET 3 [51]		
Pazienti con diabete di tipo 2 in trattamento con insulina basale, metformina±altri ipoglicemizzanti orali e $HbA1_c$ 7,5-9,5%.	Studio doppio cieco, 2 braccia di trattamento: 1. Faster Aspart (meal-time)+Glargine+Metformina 2. Glargine+Metformina Durata dello studio 18 settimane.	- Faster Aspart meal-time si associa ad una maggiore riduzione della $HbA1_c$ rispetto a Glargine; - Faster Aspart meal-time si associa ad una maggiore riduzione delle glicemie domiciliari; - Faster Aspart+Glargine si associa ad un atteso maggior numero di eventi ipoglicemici rispetto alla sola Glargine.
ONSET 4 [52]		
Pazienti con diabete di tipo 1 in trattamento con CSII e $HbA1_c$ ≤ 9%.	Studio doppio cieco, 2 braccia di trattamento: 1. Faster Aspart 2. Aspart Durata dello studio 6 settimane	- Non sono stati osservati episodi microscopicamente confermati di occlusione del set di infusione - Faster Aspart come Aspart ha fornito un efficace controllo glicemico.

ONSET 5 [43]		
Pazienti con diabete di tipo 1 in trattamento con CSII e $HbA1_c$ 7-9%.	Studio doppio cieco, 2 braccia di trattamento: 1. Faster Aspart 2. Aspart Durata dello studio 16 settimane	- Faster Aspart non è inferiore rispetto ad Aspart nel ridurre la $HbA1_c$ - Faster Aspart si associa ad una maggiore riduzione della glicemia postprandiale dopo 30 minuti, 1 ora e 2 ore rispetto alla Aspart al meal test - Profilo di sicurezza sovrapponibile (numero totale di ipoglicemie)
ONSET 7 [49]		
Pazienti con diabete di tipo 1 (bambini e adolescenti) in trattamento basal bolus e $HbA1_c$ ≤9,5%.	Studio doppio cieco, 3 braccia di trattamento di cui 1 open label (post – meal): 1. Faster Aspart (meal-time)+ Degludec 2. Aspart (meal-time)+Degludec 3. Faster Aspart (post-meal)+Degludec Durata dello studio 26 settimane	- Faster Aspart meal-time è superiore ad Aspart nel ridurre la $HbA1_c$ - Faster Aspart post-meal non è inferiore rispetto ad Aspart nel ridurre la $HbA1_c$ - Faster Aspart meal- time si associa ad una maggiore riduzione della glicemia postprandiale dopo 1 ora, dopo tutti i pasti, rispetto ad Aspart (glicemie domiciliari) - Profilo di sicurezza sovrapponibile (numero totale di ipoglicemie)
ONSET 8 [46]		
Pazienti con diabete di tipo 1 in trattamento basal bolus e $HbA1_c$ 7-9,5%.	Studio doppio cieco, 3 braccia di trattamento di cui 1 open label (post – meal): 1. Faster Aspart (meal-time)+Degludec 2. Faster Aspart (post-meal)+Degludec 3. Aspart (meal-time)+Degludec Durata dello studio 26 settimane.	- Faster Aspart meal-time o post-meal non è inferiore rispetto ad Aspart nel ridurre la HbA_{1c}; - Faster Aspart meal-time si associa ad una maggiore riduzione della glicemia postprandiale dopo 30 min e 1 ora rispetto alla Aspart al meal test; - Profilo di sicurezza sovrapponibile (numero totale di ipoglicemie).
ONSET 9 [53]		
Pazienti con diabete di tipo 2 in trattamento basal bolus±altri ipoglicemizzanti orali e $HbA1_c$ 7-10%.	Studio doppio cieco, 2 braccia di trattamento: 1. Faster Aspart (meal-time)+Degludec ± metformina 2. Aspart (meal-time)+Degludec ± met Durata dello studio 16 settimane	- Faster Aspart non è inferiore rispetto ad Aspart nel ridurre la $HbA1_c$; - Faster Aspart si associa ad una maggiore riduzione della glicemia postprandiale dopo 1 ora rispetto alla Aspart al meal test - Faster Aspart si associa a una diminuzione significativa di eventi ipoglicemici (numero totale di ipoglicemie) rispetto ad Aspart

Investigation of Pump Compatibility of Fast-Acting Insulin Aspart in Subjects With Type 1 Diabetes

Table 2. Evaluation of the Infusion Sets During the Trial.

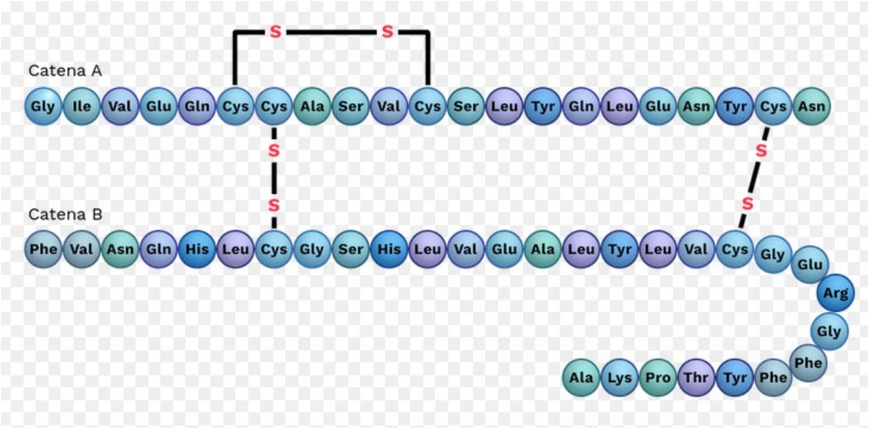
Type of change	Faster aspart	Insulin aspart	Total	Evaluation
Routine at home	210	98	308	Macroscopic by subject
Routine at site visit	147	72	219	Macroscopic and microscopic by laboratory
Premature	21	4	25	Macroscopic by subject; plus macroscopic and microscopic by laboratory if shipped[a]
Unclassified	1	0	1	Macroscopic by subject
Total	379	174	553	

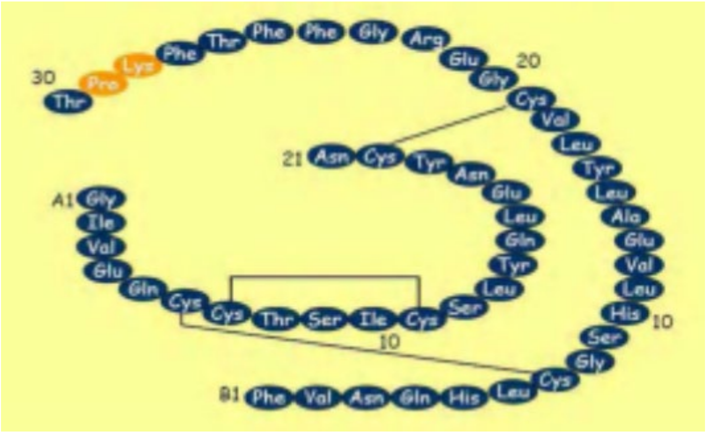
[a]Three of the seven infusion sets that were changed prematurely because of a possible occlusion were shipped to the laboratory for macroscopic and microscopic evaluation (all in the faster aspart group).

No microscopically confirmed episodes of infusion-set occlusions were observed in either of the treatment arms after 6 weeks of treatment.

Zijlstra E et al. J Diabetes Sci Technol 2018;12:145-151

Ultra rapid lispro insulin: la struttura molecolare





Insulin lispro enriched with two excipients:

✓Treprostinil (promotes local vasodilation)

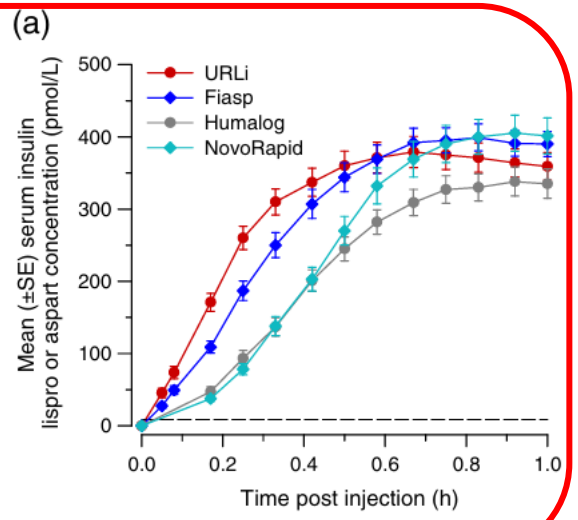
✓Citrate (enhances local vascular permeability)

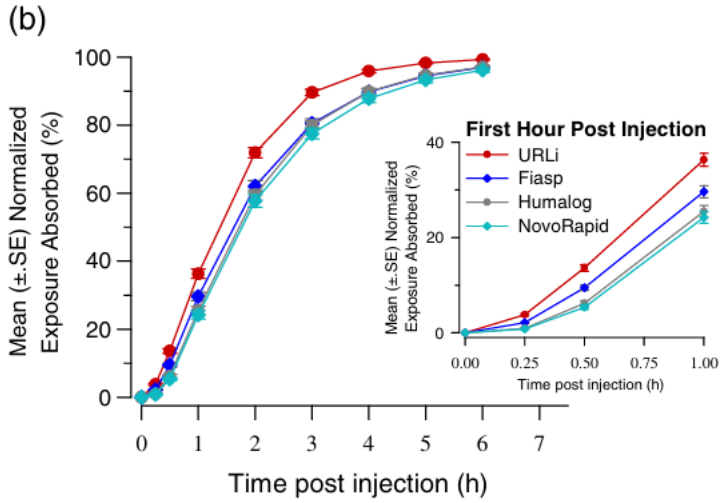
Ultra rapid lispro lowers postprandial glucose and more closely matches normal physiological glucose response compared to other rapid insulin analogues: A phase 1 randomized, crossover study

5.9 minutes faster than Fiasp

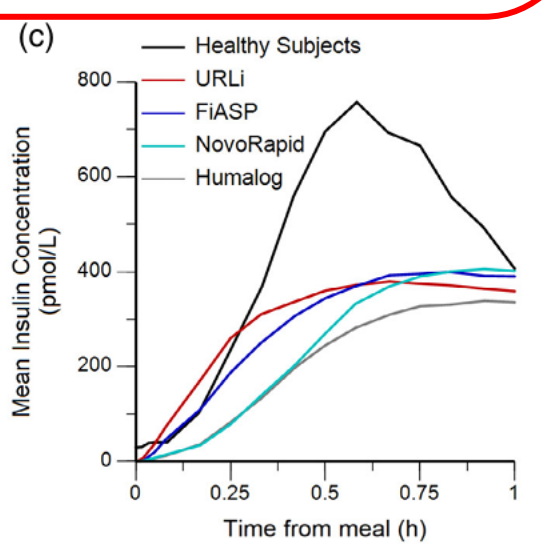
12.5 minutes faster than Humalog

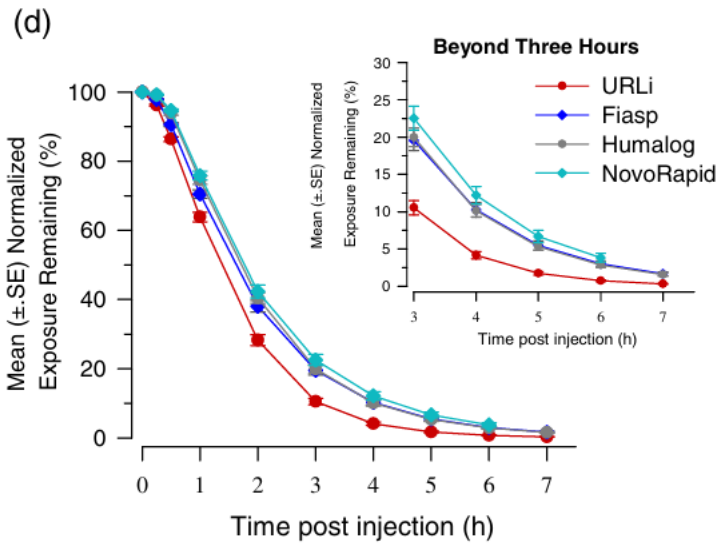
13.9 minutes faster than NovoRapid



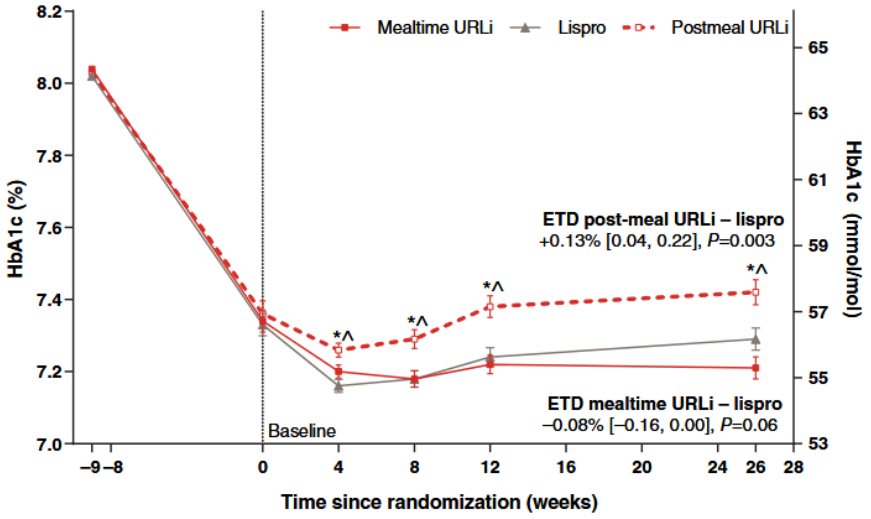


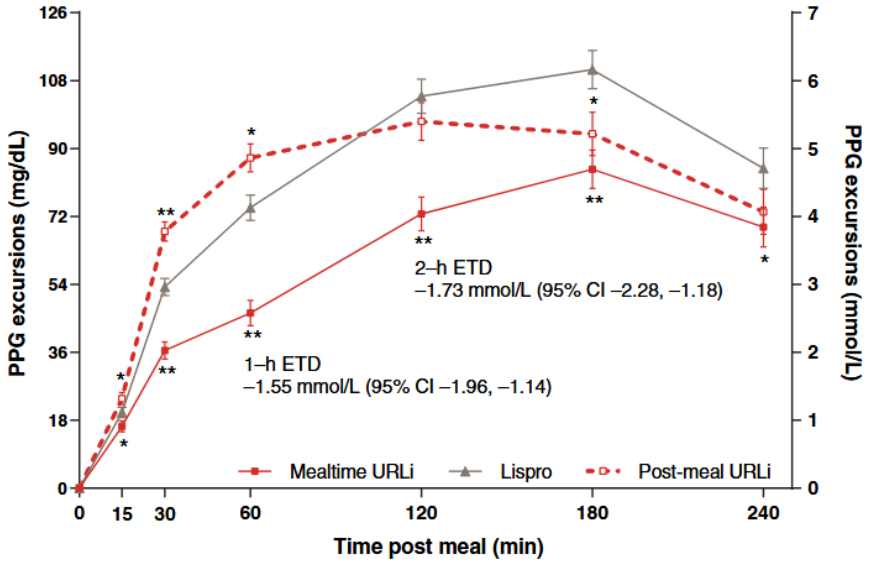
The early 50% tmax was reached 12.8 minutes after URLi administration

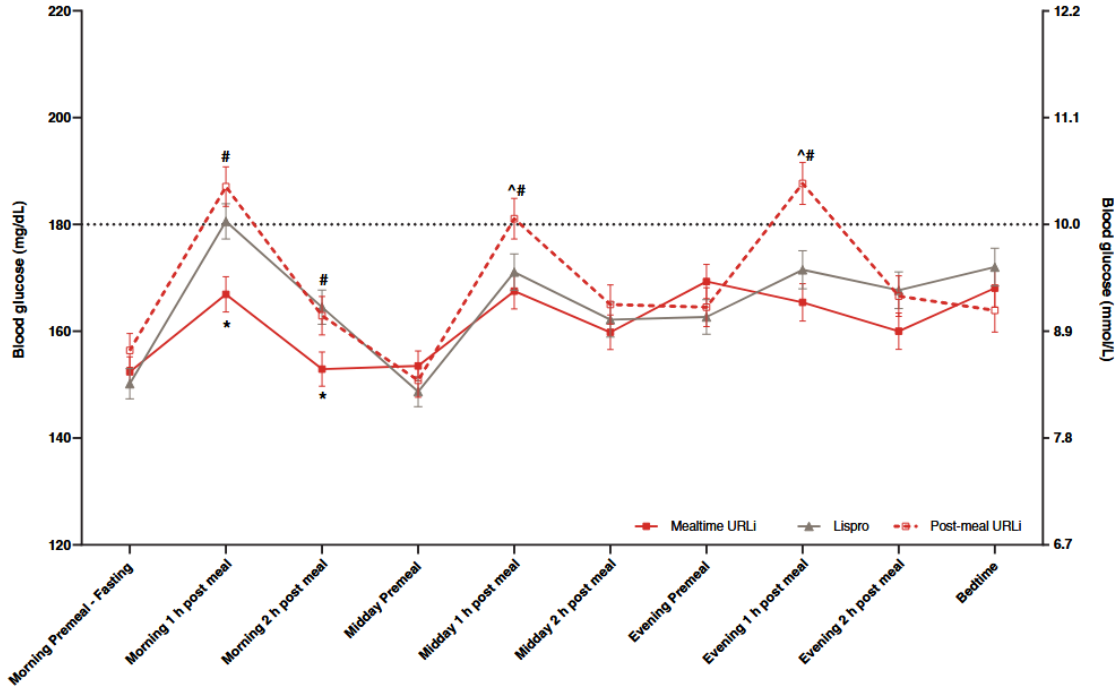


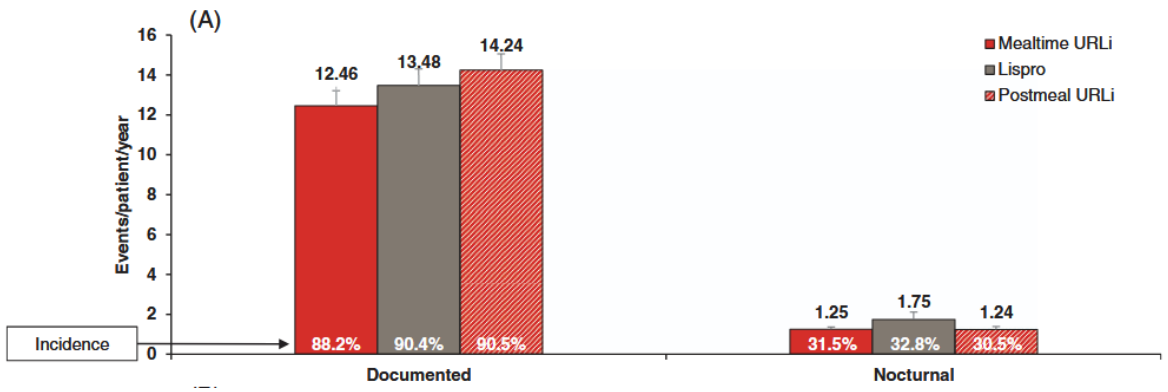


Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: Results from the 26-week PRONTO-T1D study

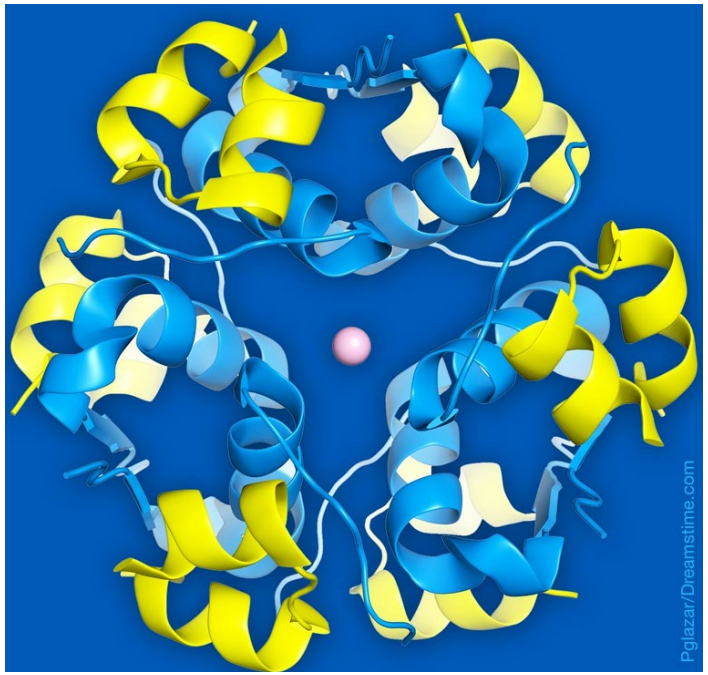








Klaff L et al. Diabetes Obes Metab 2020;22:1799-1807



Inhaled technosphere insulin

- Is a second-generation inhaled insulin featuring microparticles made of fumaryl diketopiperazine. These microparticles form microspheres that possess the ideal size of 2-3 um necessary for absorbing drug particles into the alveoli.
- Conventional human insulin is incorporated into these microspheres, whichare subsequently freeze-dried into a dry powder, facilitating inhalation.
- Reaches peak levels within 11-23 min of inhalation
- Peak activity around an hour after administration
- Terminal half-life of 1 h

Inhaled Technosphere Insulin: A Novel Delivery System and Formulation for the Treatment of Types 1 and 2 Diabetes Mellitus

Anne J. Kugler,[1,2,*] Kristin L. Fabbio,[3,4] David Q. Pham,[1,5] and Daniel A. Nadeau[5]

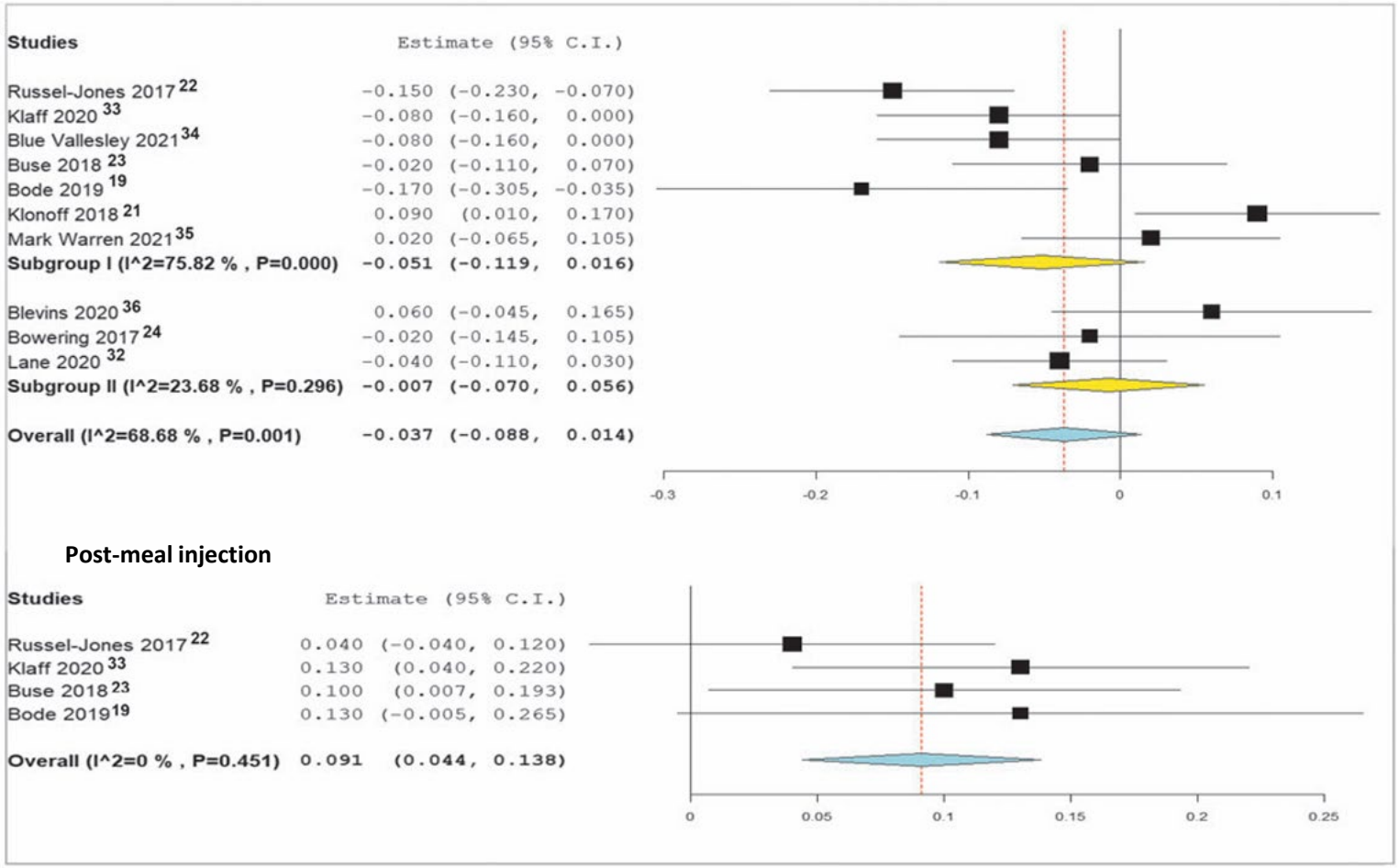
[1]Department of Pharmacy Practice and Administration, College of Pharmacy, Western University of Health Sciences, Pomona, California; [2]St. Mary's Medical Center, Long Beach, California; [3]Division of Pharmacy Practice, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, New York; [4]Kings County Hospital Center, Brooklyn, New York; [5]Mary & Dick Allen Diabetes Center, Hoag Hospital, Newport Beach, California

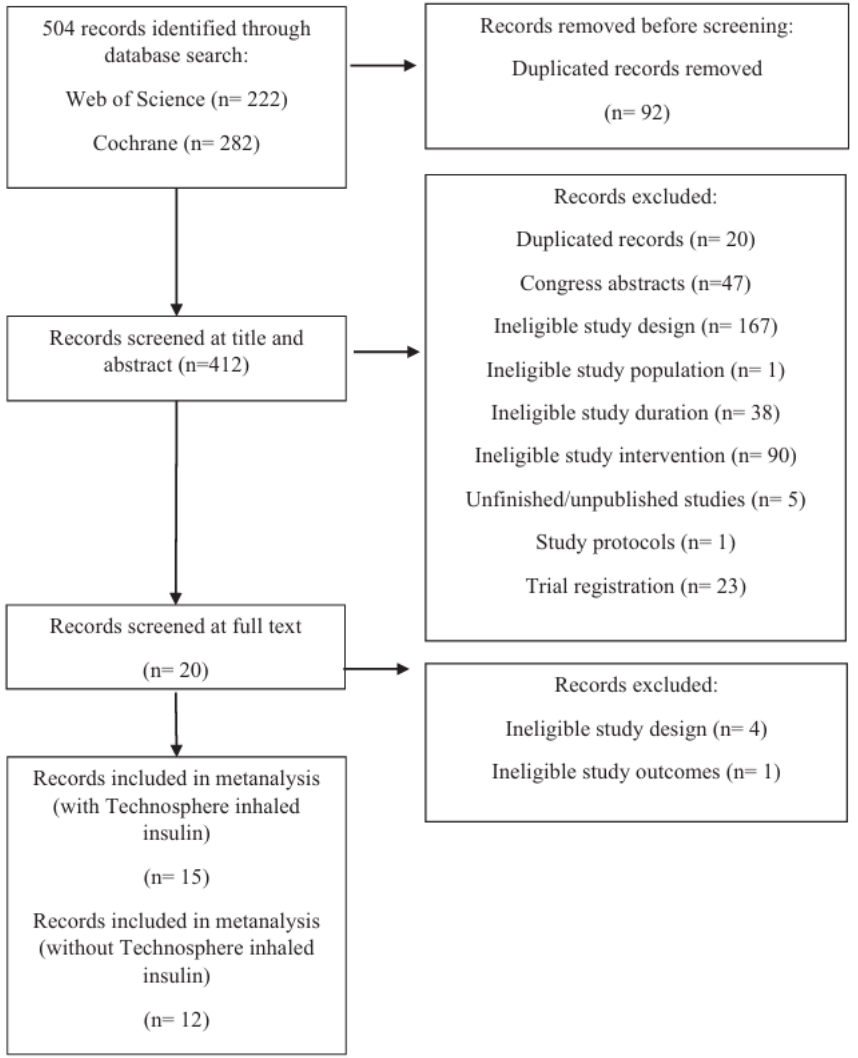
Population	Study design (duration)	Study arms	Baseline A1C, mean ± SD %	Change in A1C from baseline		Change in FPG level		2-hr postprandial blood glucose level		Achieved A1C ≤ 7%		Dropout rate, no. (%)
				Mean %	95% CI or p value for difference vs control	Mean change, mg/dl	p value for difference vs control	Mean level, mg/dl	p value for difference vs control	% of patients	p value for difference vs control	
Affinity 1 T1DM (n=518) [b,33, 34]	Randomized, open-label, forced-titration, noninferiority (24 wks)	TI (Dreamboat) + basal insulin	7.98 ± 0.767	−0.21	0.02–0.36	−25.27	p=0.0009	NR		18.3	p=0.0158	44 (25.3)
		Aspart + basal insulin	7.88 ± 0.751	−0.40		10.15				30.7		19 (11.2)
		TI (MedTone) + basal insulin	7.99 ± 0.732	NA		NA				NA		36 (20.7)
Affinity 2 T2DM (n=353) [b,33, 35]	Randomized, double-blind, placebo-controlled, forced-titration (24 wks)	TI (Dreamboat) + OADs	8.26 ± 0.680	−0.82	−0.57 to −0.23	−11.20	p=0.1698	NR		32.2	p=0.0002	27 (15.3)
		Technosphere powder (placebo) + OADs	8.35 ± 0.775	−0.42		−3.78				15.3		37 (21.0)

Pharmacotherapy 2015;35:298–314

Are New Ultra-Rapid-Acting Insulins Associated with Improved Glycemic Control and Reduced Hypoglycemia in Comparison to Conventional Rapid-Acting Insulins for Individuals with Type 1 and Type 2 Diabetes? A Systematic Review and Meta-Analysis

HbA1c





Villar-Taibo R et al Diabetes Technol Ther 2024;26:575-586

Are New Ultra-Rapid-Acting Insulins Associated with Improved Glycemic Control and Reduced Hypoglycemia in Comparison to Conventional Rapid-Acting Insulins for Individuals with Type 1 and Type 2 Diabetes? A Systematic Review and Meta-Analysis

Hypoglycemia

The rate of severe or confirmed hypoglycemia did not differ between the mealtime ultra-rapid analog group and the rapid-acting analog group

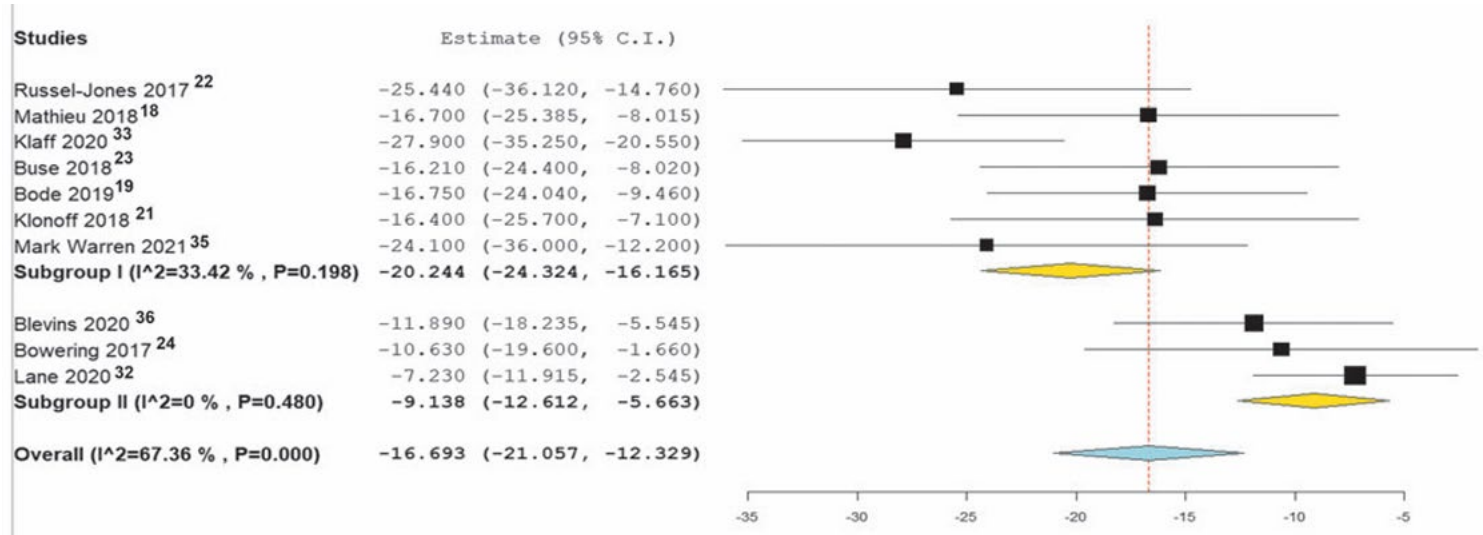
0.978 [95% CI 0.944 to 1.014]; p=0.23

Similarly, in the subgroup analysis:

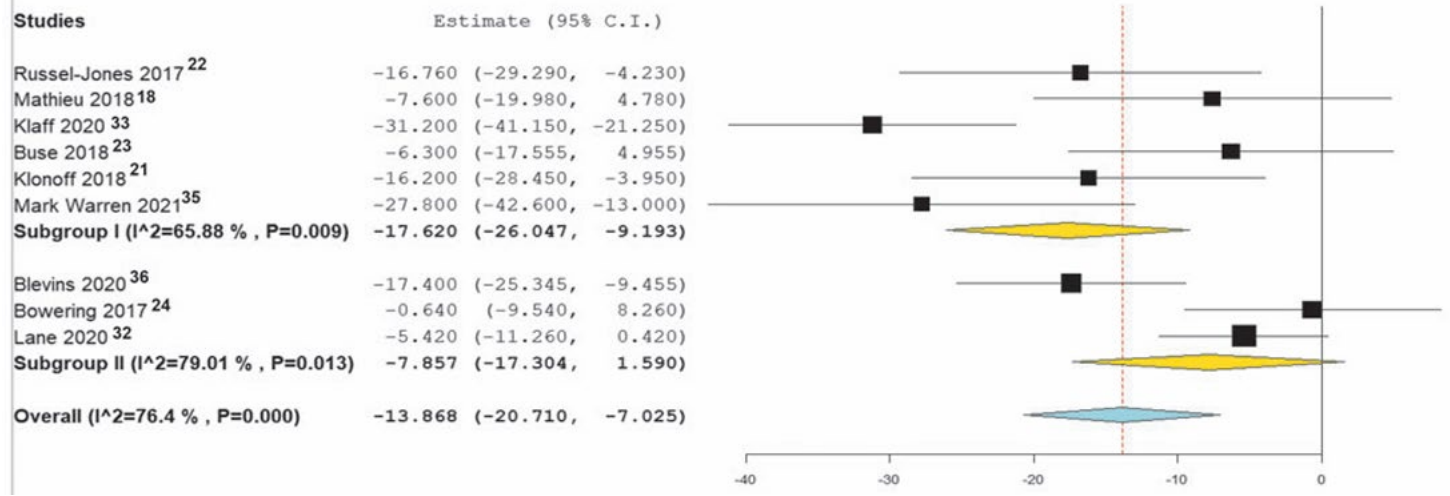
T1D (0.982 [95%CI 0.946-1.020]; p=0.35)

T2D (0.956 [95%CI 0.793-1.151]; p=0.63)

1h postprandial glucose values



2h postprandial glucose values



Villar-Taibo R et al Diabetes Technol Ther 2024;26:575-586

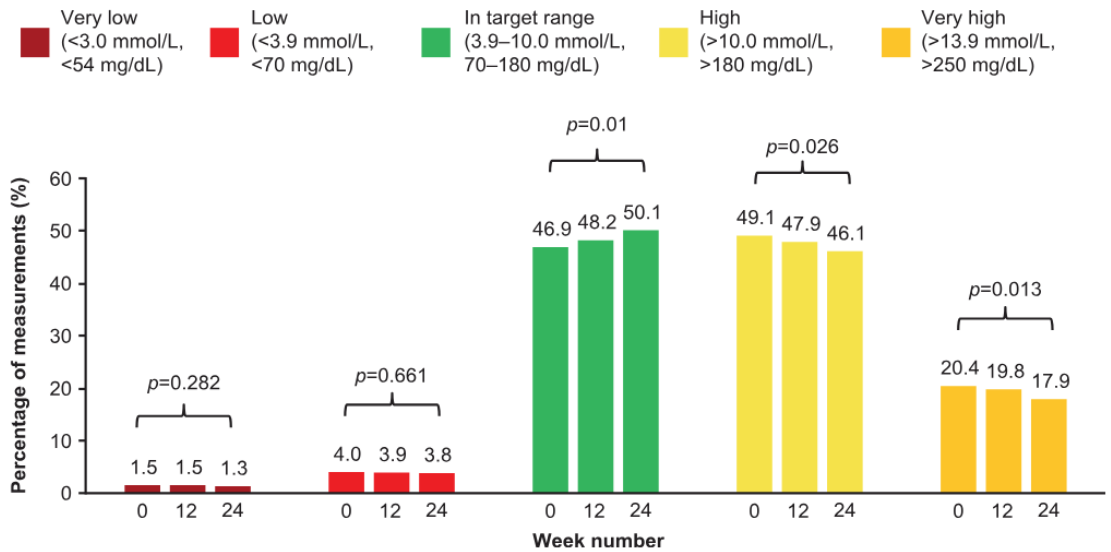
DIABETES TECHNOLOGY & THERAPEUTICS
Volume 23, Number 3, 2021
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2020.0360

DTT

ORIGINAL ARTICLE

Impact of Fast-Acting Insulin Aspart on Glycemic Control in Patients with Type 1 Diabetes Using Intermittent-Scanning Continuous Glucose Monitoring Within a Real-World Setting: The GoBolus Study

Thomas Danne, MD,[1] Matthias Axel Schweitzer, MD,[2] Winfried Keuthage, MD,[3] Stefan Kipper, MS,[2] Yasmin Kretzschmar, MD,[2] Jörg Simon, MD,[4] Tanja Wiedenmann, PhD,[2] and Ralph Ziegler, MD[5]



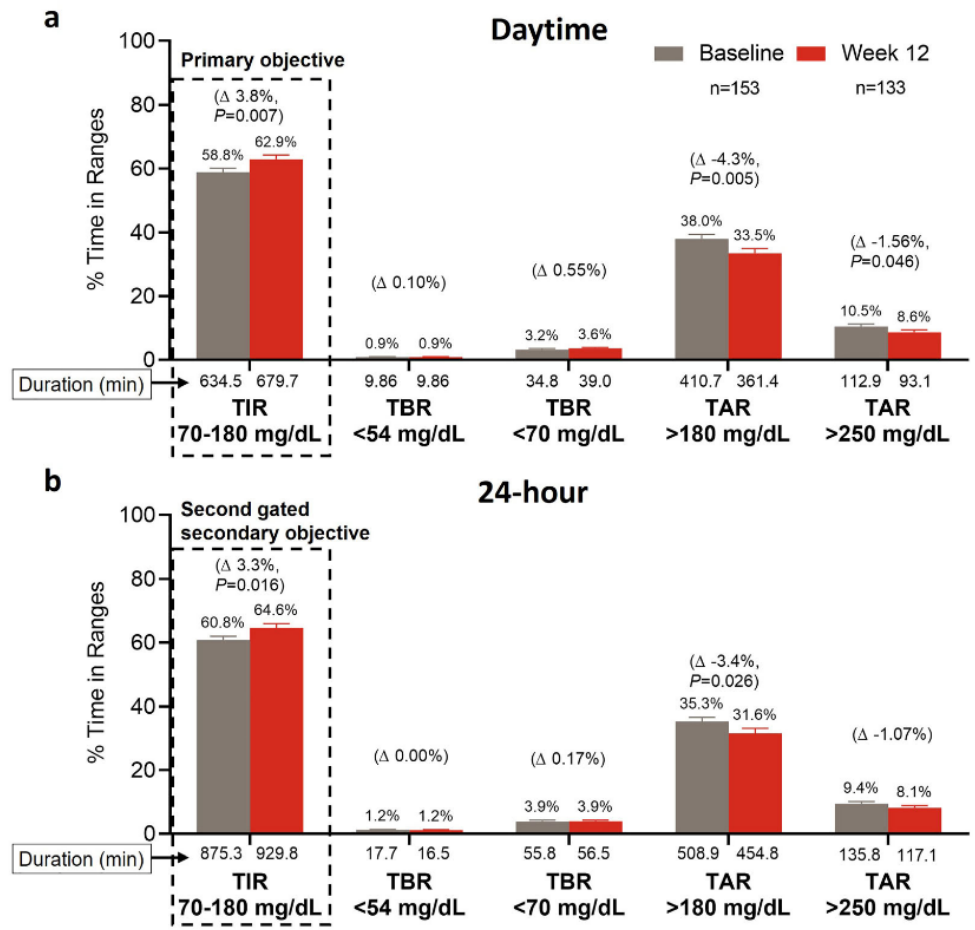
Diabetes Ther (2023) 14:883–897
https://doi.org/10.1007/s13300-023-01400-w

Check for updates

ORIGINAL RESEARCH

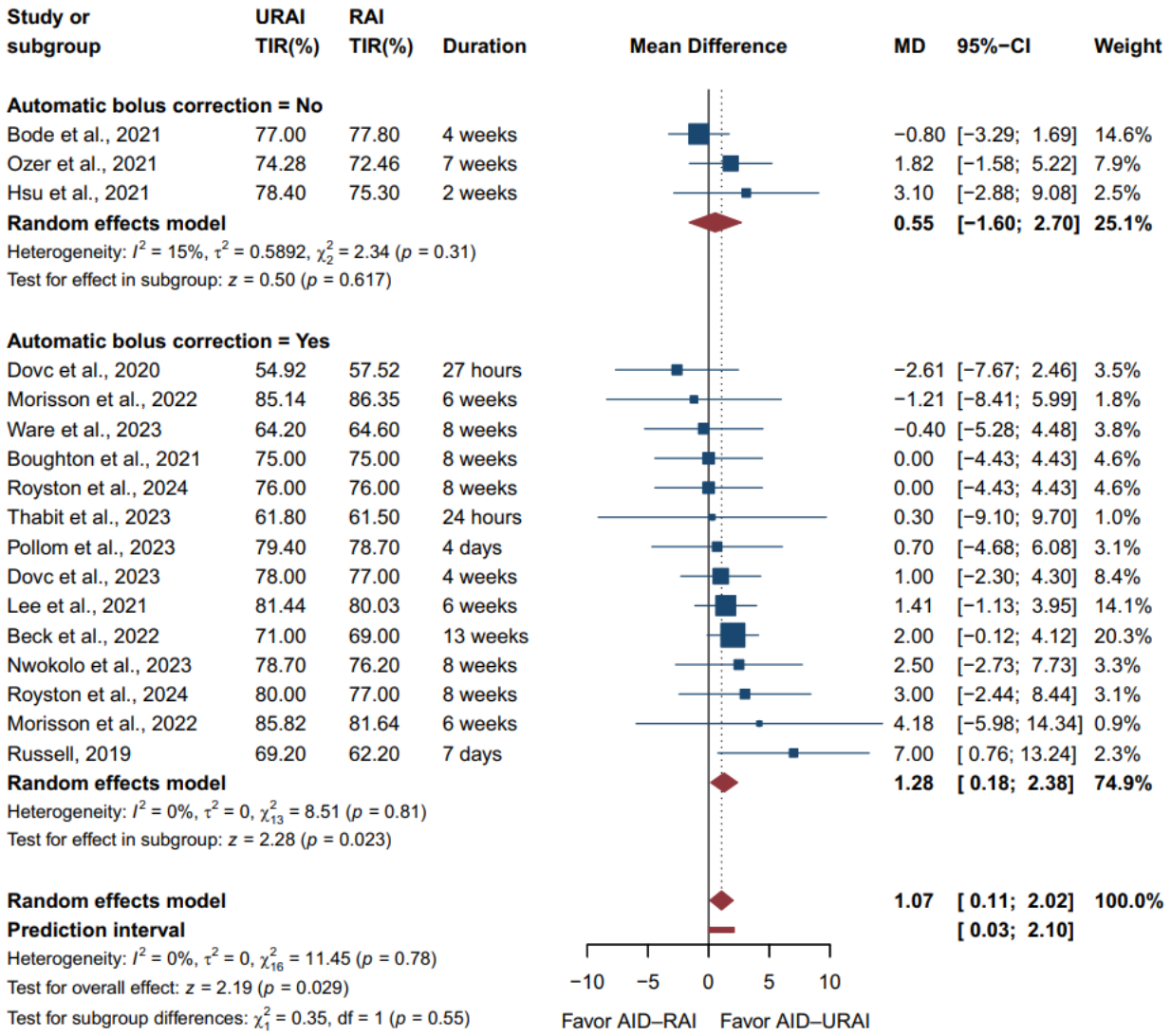
Increased Time in Range with Ultra Rapid Lispro Treatment in Participants with Type 2 Diabetes: PRONTO-Time in Range

Timothy S. Bailey · Bruce W. Bode · Qianqian Wang · Alastair W. Knights · Annette M. Chang



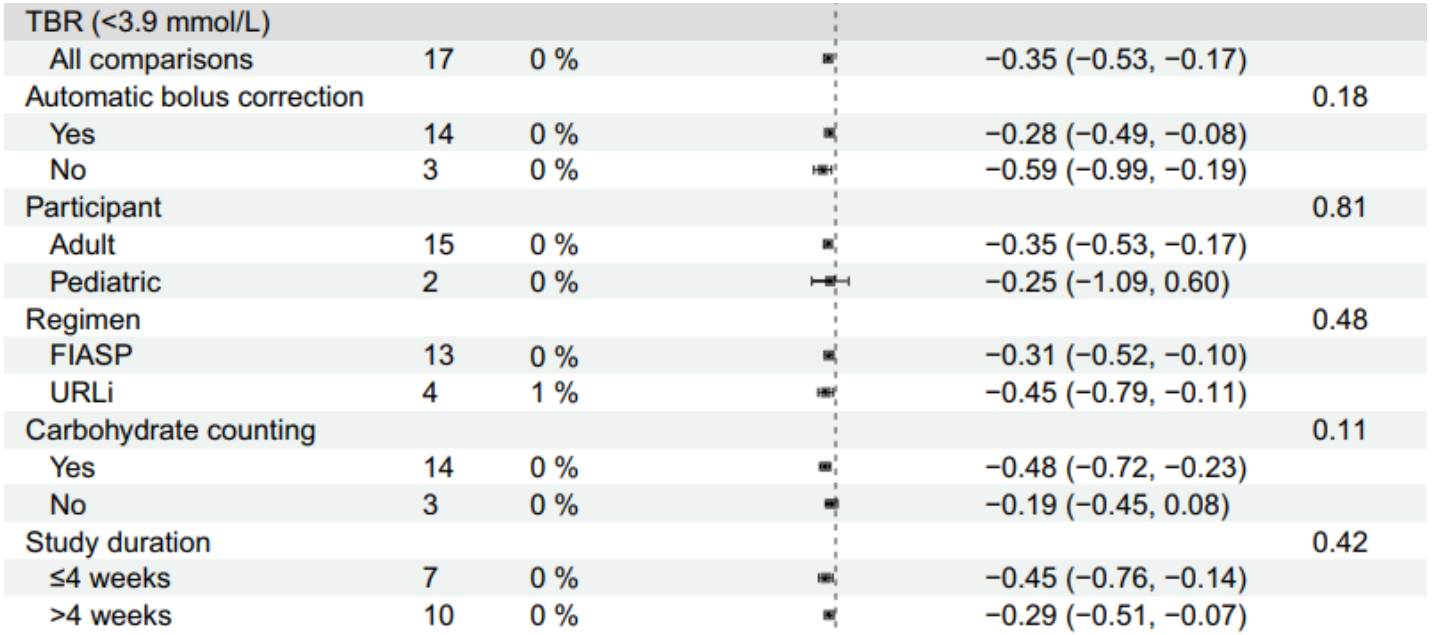
A comparison of ultra-rapid and rapid insulin in automated insulin delivery for type 1 diabetes: A systematic review and meta-analysis of randomized controlled trials

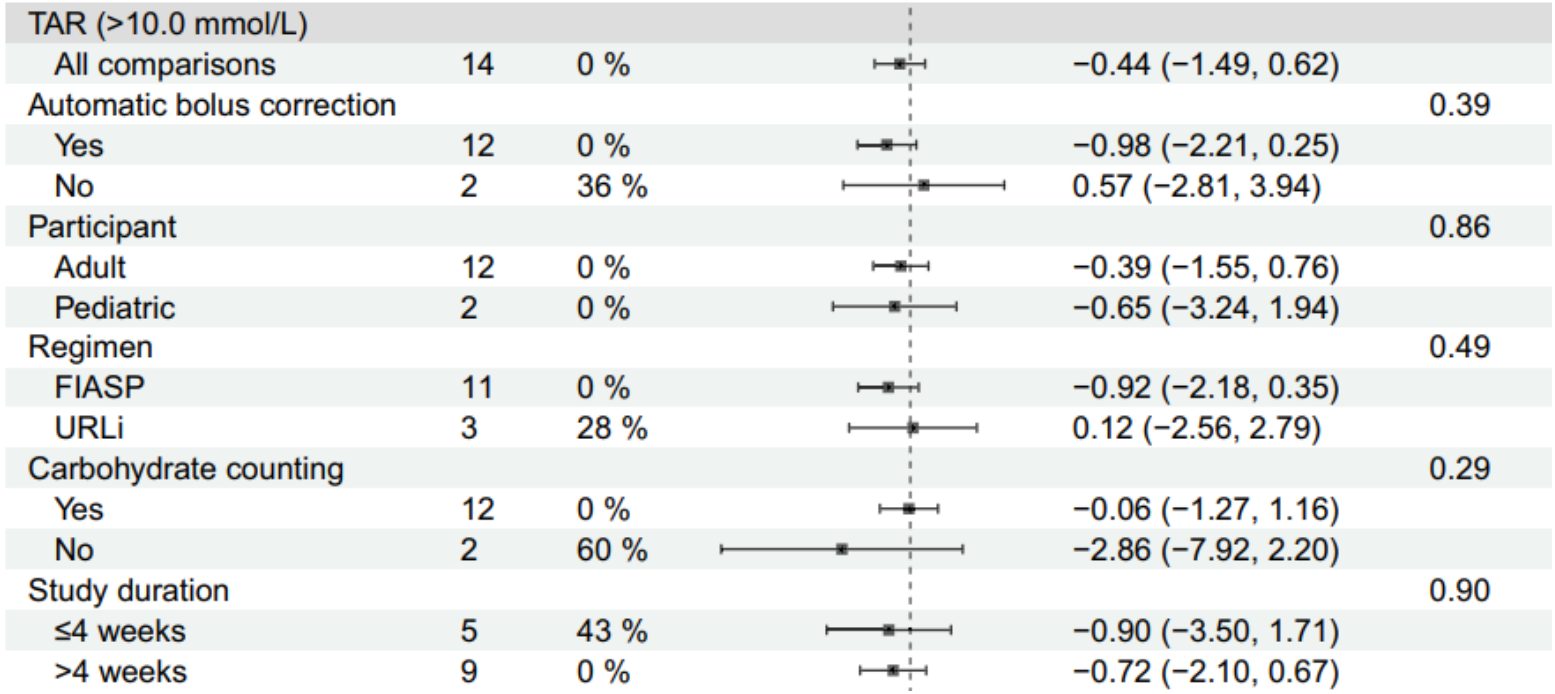
Puguh Oktavian MD[1] | Citrawati Dyah Kencono Wungu PhD[2,3] | Sony Wibisono Mudjanarko PhD[4] | Indah Mohd Amin PhD[5]



Oktavian P et al. DOM 2025;27:2658-2669

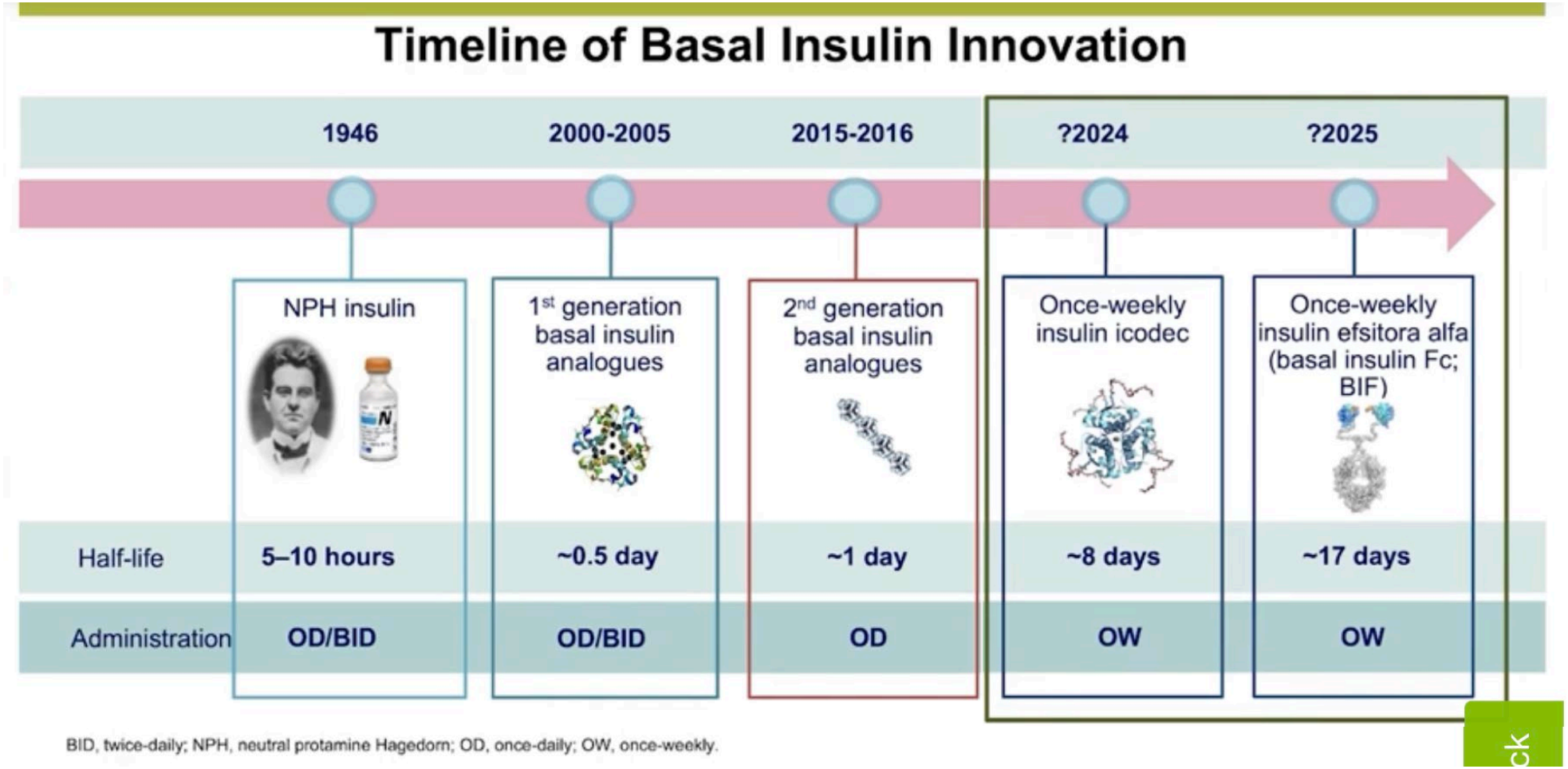
A comparison of ultra-rapid and rapid insulin in automated insulin delivery for type 1 diabetes: A systematic review and meta-analysis of randomized controlled trials





Oktavian P et al. DOM 2025;27:2658-2669

Le nuove insuline ultralente



Insuline Ultra-Long-Acting: Razionale

Riduzione burden terapeutico:
da 365 a 52 iniezioni/anno

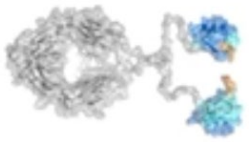
Miglioramento della qualità di vita

Maggiore aderenza e persistenza terapeutica

Miglioramento outcome a breve e lungo termine

Insuline Ultra-Long-Acting: quali molecole?

Efsitora Alfa (BIF)

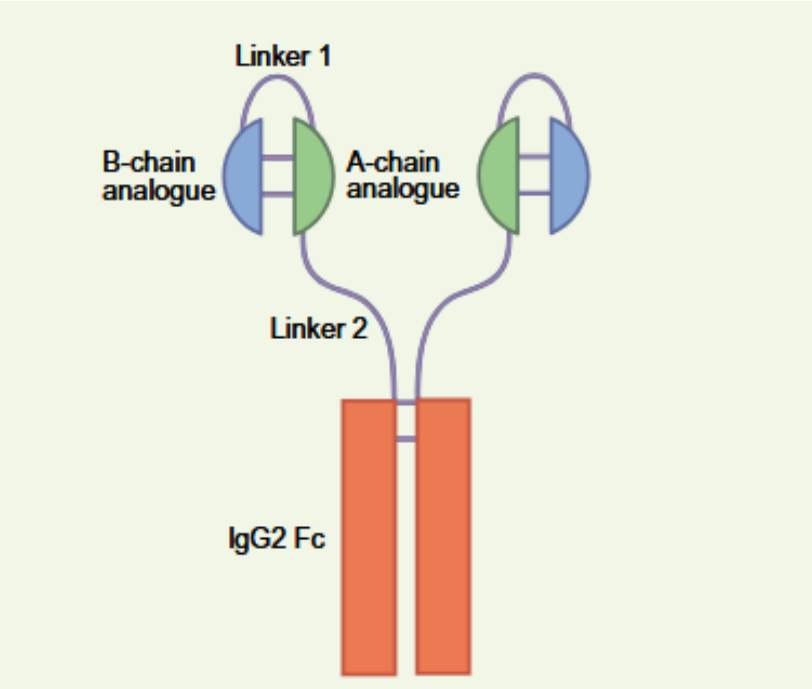


- Variante insulinica a singola catena
- **Fusione covalente** con dominio **Fc di IgG2** umana
- **QWINT** trial program

Icodec

- Nuovo analogo insulinico coniugato con acido grasso
- **Legame reversibile** con **albumina** circolante
- **ONWARDS** trial program

Efsitora Alfa (BIF)

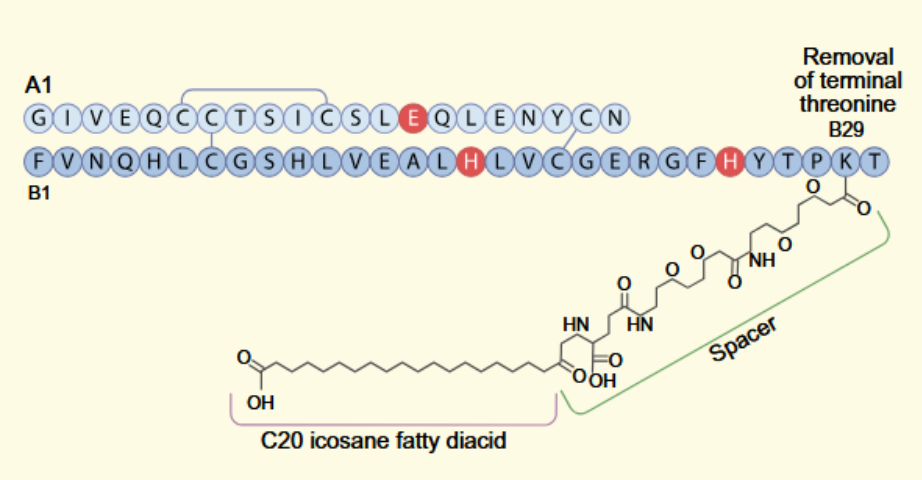


Omodimero selettivo per il **recettore insulinico (IR)**

Emivita di 17 giorni grazie a **4 meccanismi:**

- **Lento assorbimento** dal tessuto sottocutaneo
- **Rallentata clearance** renale
- **Riciclo** mediato dalla via di recupero della porzione Fc dell'Ig
- **Ridotta affinità** di legame per IR

Icodec



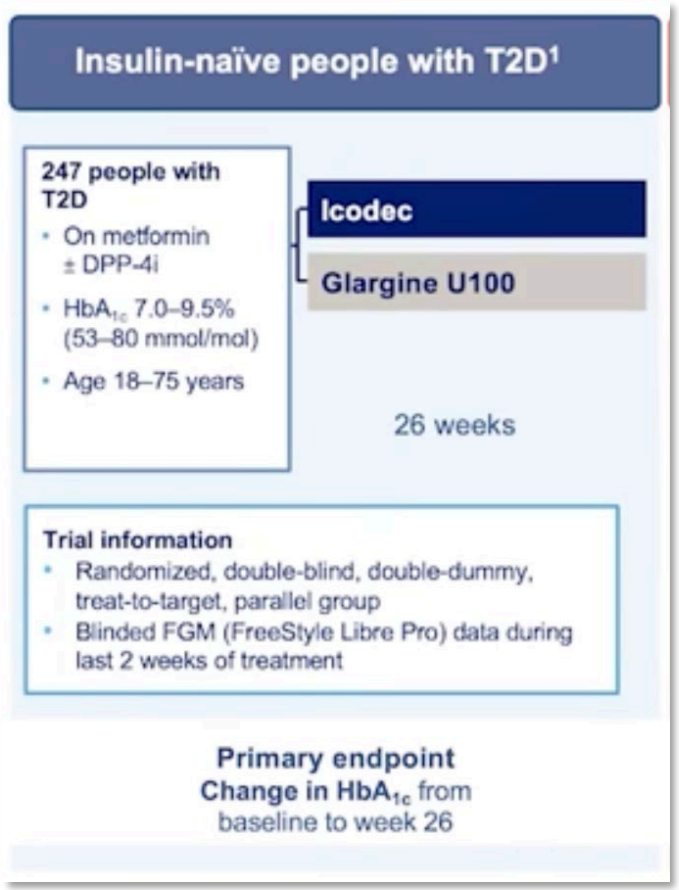
Analogo insulinico coniugato con **acido grasso C20**

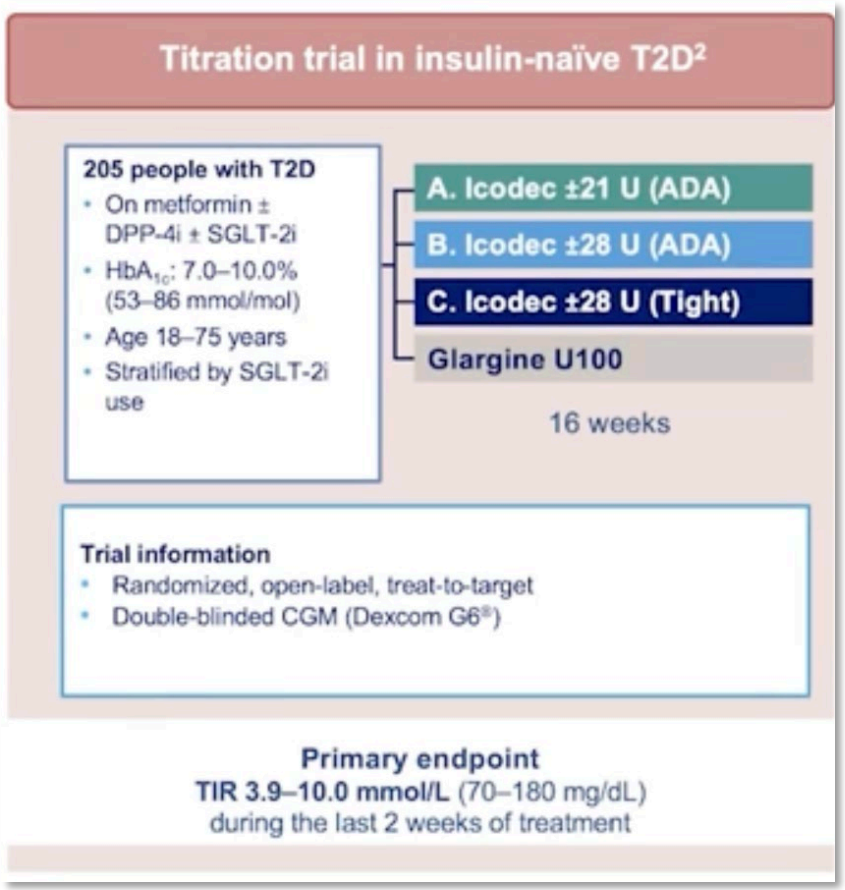
3 sostituzioni aminoacidiche:
- Rallentata degradazione
- Ridotta affinità per IR
- Aumento solubilità (700UI/ml)

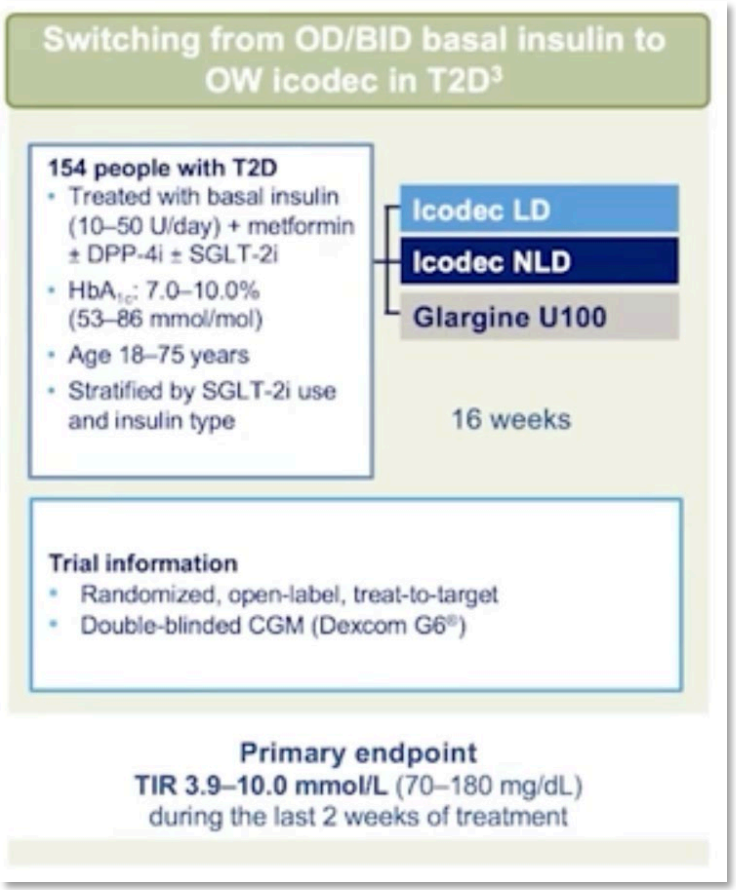
Acido grasso C20:
- Legame reversibile con albumina
- Ridotta affinità relativa con IR

Emivita di circa **8 giorni,** grazie a **3 meccanismi:**
- Formazione di una **riserva inattiva a lento rilascio** albumin-bound
- **Rallentata degradazione**
- **Ridotta affinità** di legame **con IR**

Icodec
Trials clinici di fase 2 - Overview





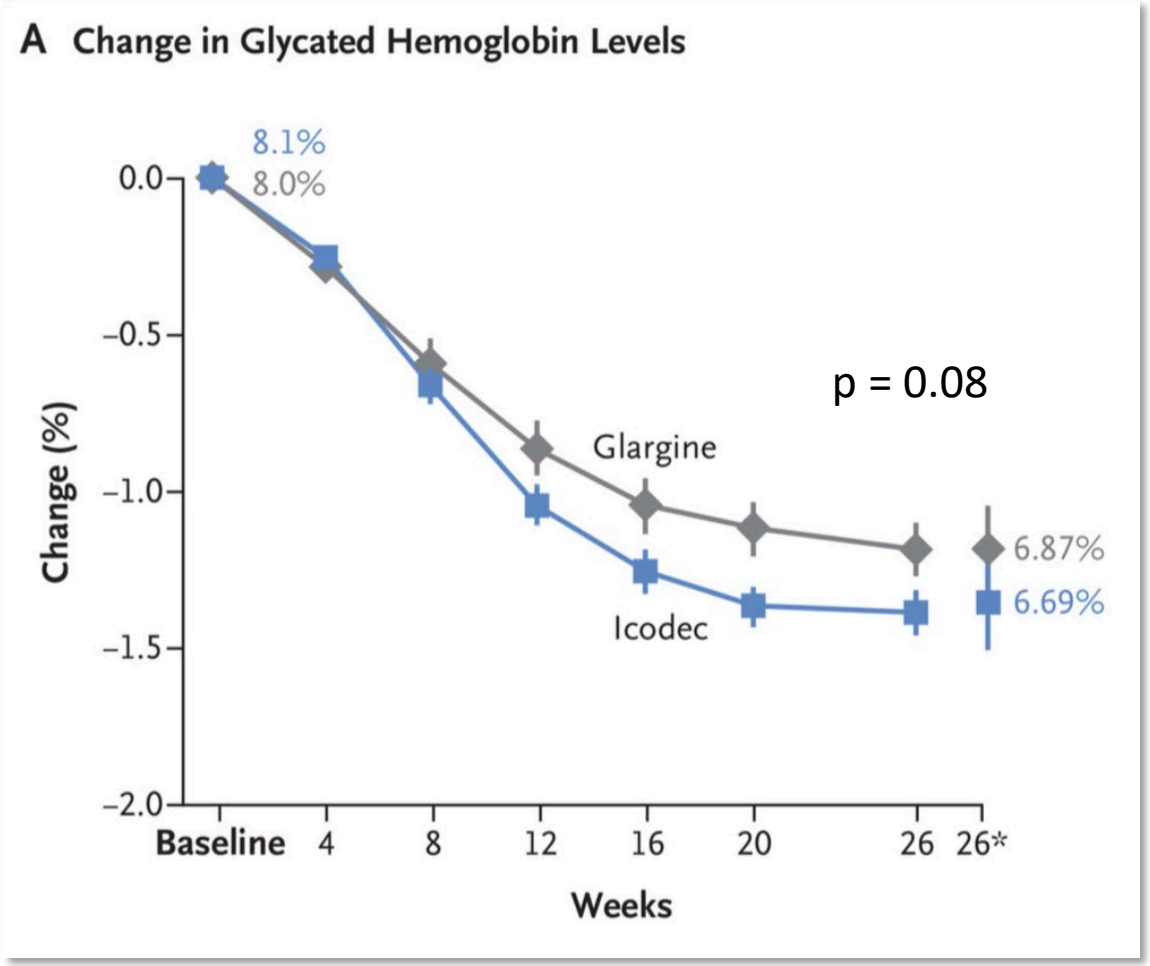


Icodec
Trials clinici di fase 2 - Outcomes

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 26, 2020 VOL. 383 NO. 22

Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment

Julio Rosenstock, M.D., Harpreet S. Bajaj, M.D., M.P.H., Andrej Janež, M.D., Ph.D., Robert Silver, M.D., Kamilla Begtrup, M.Sc., Melissa V. Hansen, M.D., Ph.D., Ting Jia, M.D., Ph.D., and Ronald Goldenberg, M.D., for the NN1436-4383 Investigators*



Efficacia:

Non inferiorità di Icodec nella **riduzione di HbA1c**

Safety:

Non differenze significative nelle **ipoglicemie di grado 2** (<54 mg/dl) **o severe**

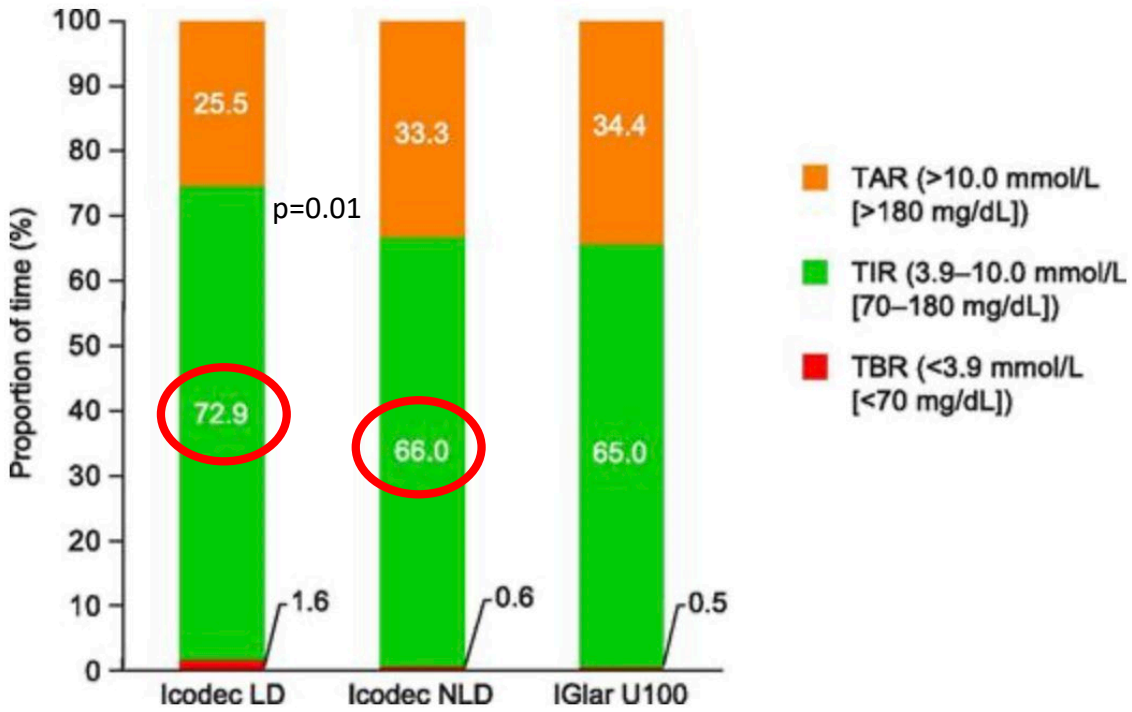
Icodec
Trials clinici di fase 2 - Outcomes

EMERGING THERAPIES: DRUGS AND REGIMENS | MARCH 19 2021

Switching to Once-Weekly Insulin Icodec Versus Once-Daily Insulin Glargine U100 in Type 2 Diabetes Inadequately Controlled on Daily Basal Insulin: A Phase 2 Randomized Controlled Trial

Harpreet S. Bajaj ; Richard M. Bergenstal ; Andreas Christoffersen; Melanie J. Davies; Amoolya Gowda; Joakim Isendahl; Ildiko Lingvay ; Peter A. Senior; Robert J. Silver; Roberto Trevisan; Julio Rosenstock

Figure 1



Icodec LD: TIR > 70%, significativamente migliore rispetto ad Icodec NLD

Icodec
Trials clinici di fase 2 - Outcomes

EMERGING THERAPIES: DRUGS AND REGIMENS | MARCH 19 2021

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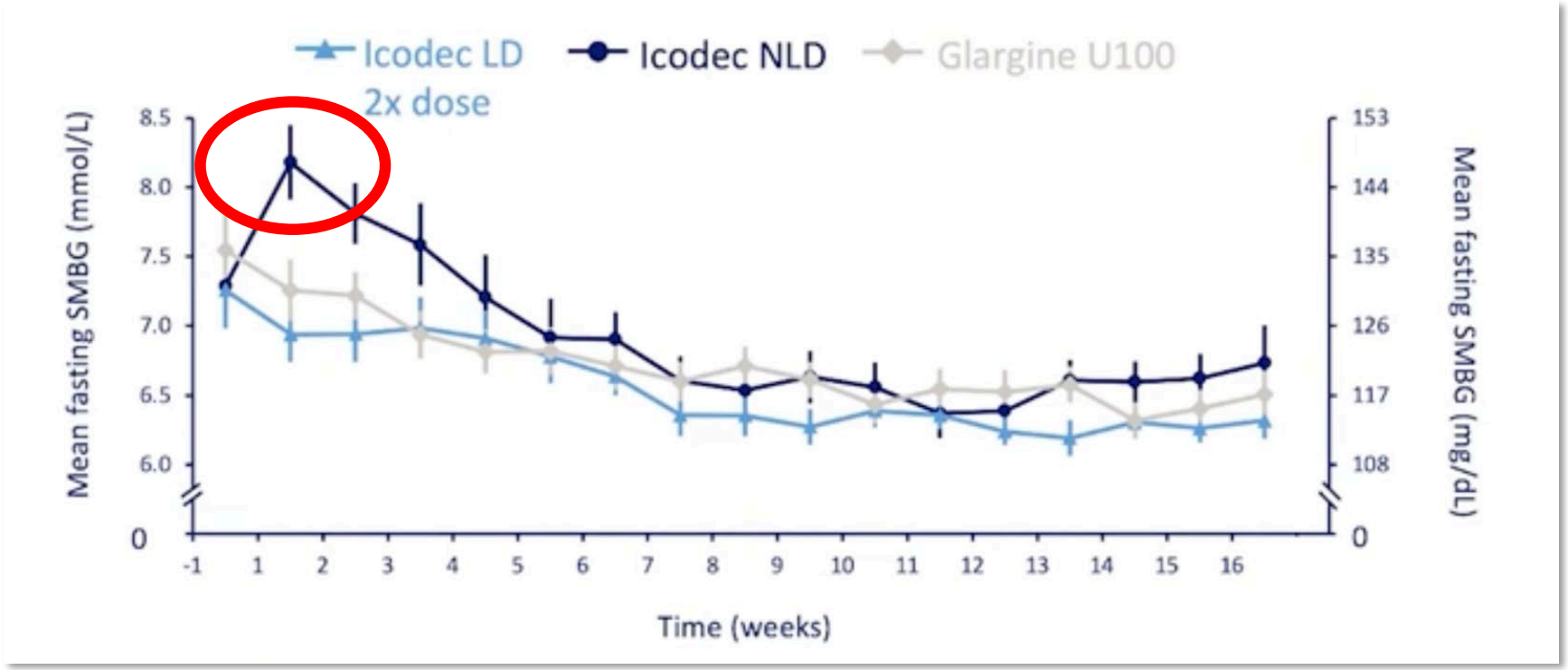
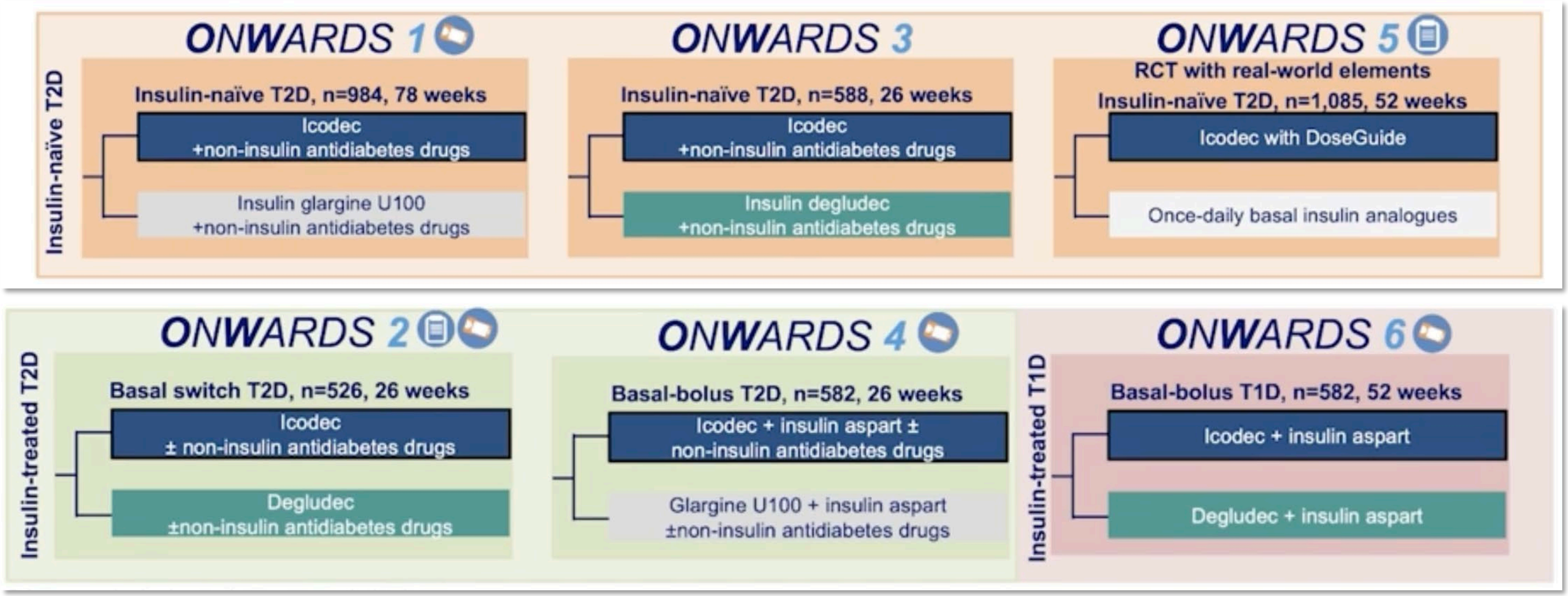


Loading Dose: dose aumentata del 50% alla prima somministrazione

ONWARDS Program



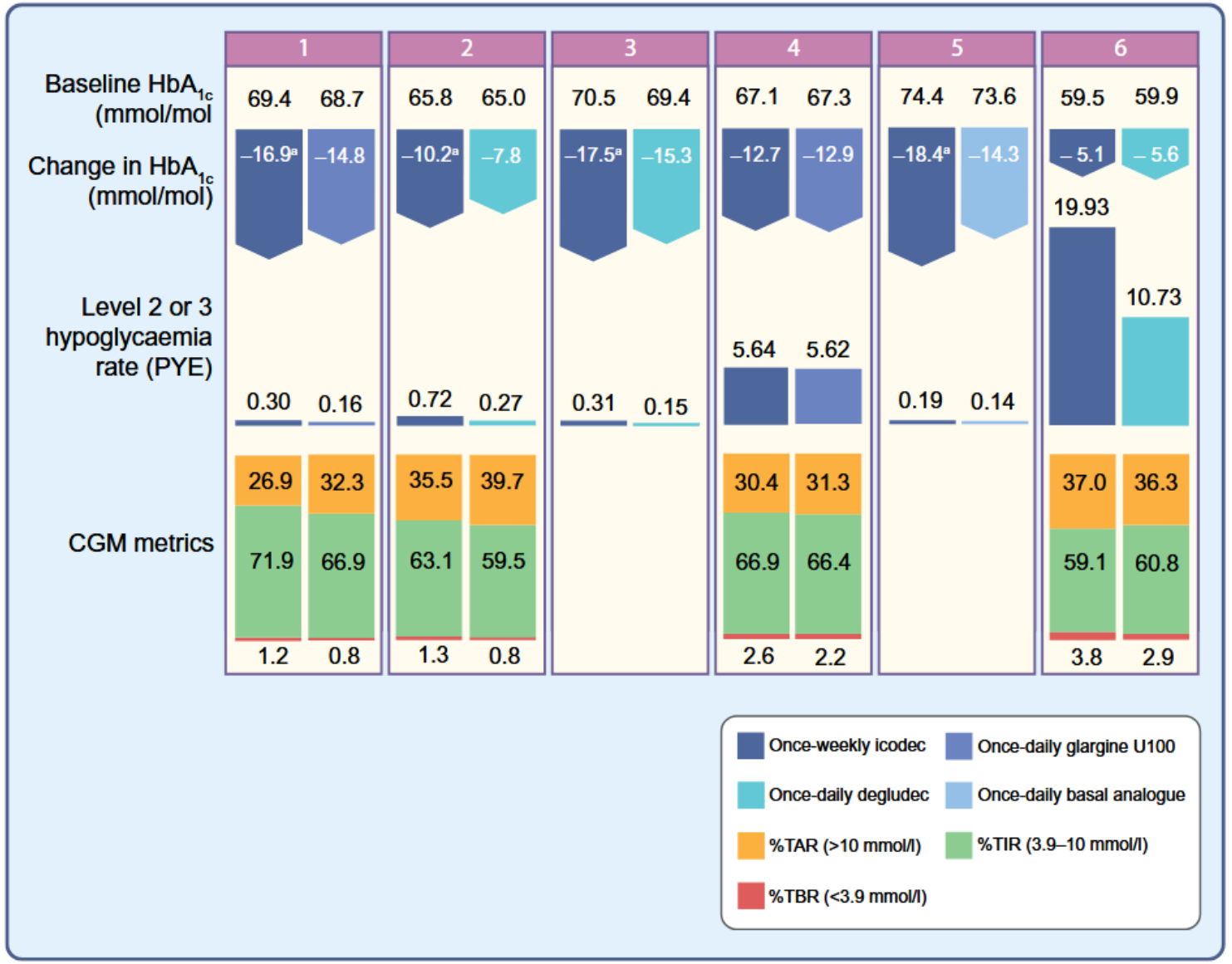
Diabetologia (2024) 67:1480–1492
https://doi.org/10.1007/s00125-024-06158-9

REVIEW

Once-weekly insulins: a promising approach to reduce the treatment burden in people with diabetes

Roberto Trevisan[1,2] · Matteo Conti[1,3] · Stefano Ciardullo[1,3]

ONWARDS Program



Trevisan R et al. Diabetologia 2024;67:1480-1492

TRIALS

ONWARDS 3

Double Blind

Treat-to-target

588 pazienti **T2D insulin-naive**, ≥ 18 anni

26 settimane

JAMA | Original Investigation

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, MD, MPH, MSCS; Marisse Asong, MD, MSc; Cyrus Desouza, MBBS; Pierre Gourdy, MD, PhD; Soumitra Kar, MSc; André Vianna, MD, PhD; Tina Vilsbøll, MD, DMsc; Siri Vinther, MD, PhD; Yiming Mu, MD

PRIMARY ASSESSMENT	CHANGE IN GLYCATED HAEMOGLOBIN (HbA_{1c}) FROM BASELINE, BETWEEN ONCE-WEEKLY ICODEC AND COMPARATOR ONCE-DAILY **DEGLUDEC**
OTHER SAFETY & EFFICACY ASSESSMENTS	FPG†; BODY WEIGHT CHANGES†; INSULIN DOSE†; HYPOGLYCAEMIC EPISODES; ADVERSE EVENTS

Primary Endpoint: riduzione di HbA1C
Icodec vs. Degludec

JAMA | Original Investigation

Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes
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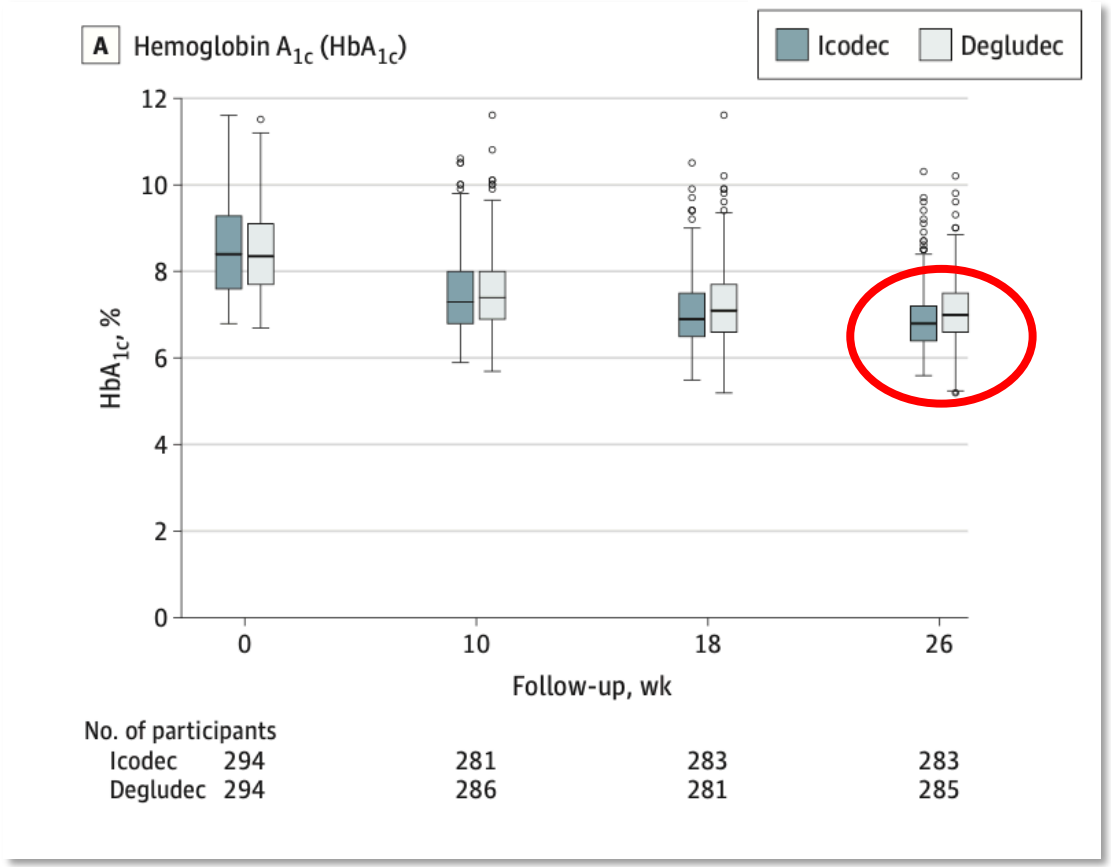


Differenza HbA1C a 26 settimane: **- 0.2%**

Non inferiorità: p<0.001
Superiorità di Icodec: p=0.002

Safety endpoints: peso, ipoglicemie
Icodec vs. Degludec

JAMA | Original Investigation

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, MD, MPH, MSCS; Marisse Asong, MD, MSc; Cyrus Desouza, MBBS; Pierre Gourdy, MD, PhD; Soumitra Kar, MSc; André Vianna, MD, PhD; Tina Vilsbøll, MD, DMsc; Siri Vinther, MD, PhD; Yiming Mu, MD

Non differenze significative nella variazione del **peso corporeo**

0 episodi di **ipoglicemia severa** con **Icodec** vs. **2** con **Degludec**

Tasso di **ipoglicemia di livello 2 o severa maggiore** per **Icodec**
(0,35 PYE vs. 0,12 PYE; p = 0.01)

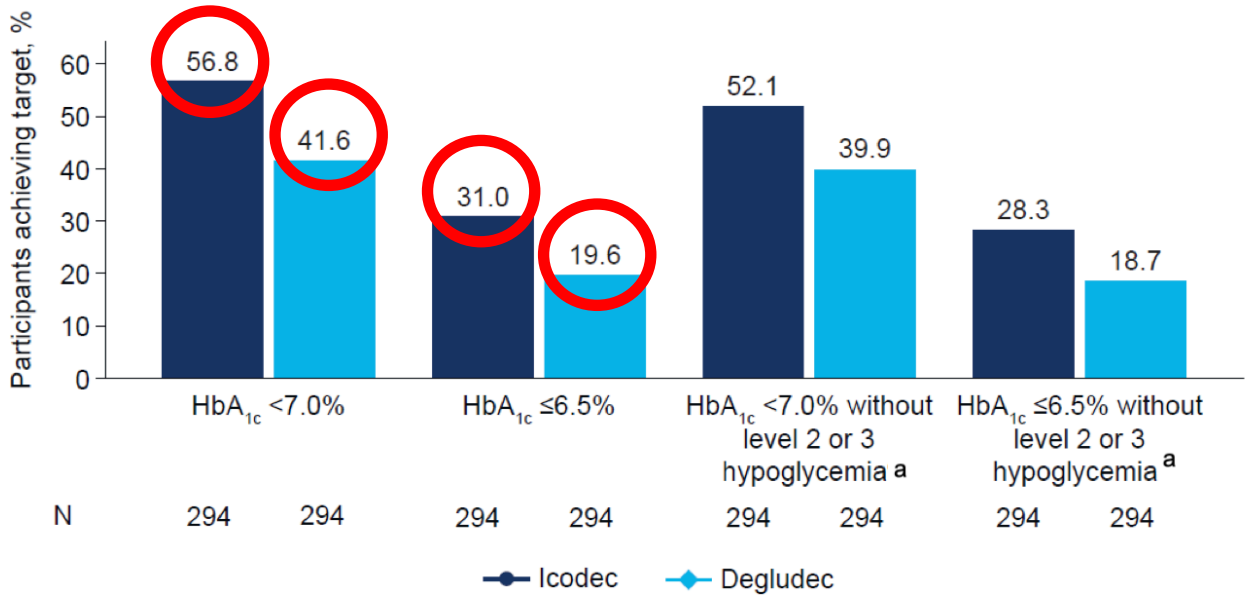
Additional Assessment: raggiungimento target HbA1c Icodec vs. Degludec

JAMA | Original Investigation

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, MD, MPH, MSCS; Marisse Asong, MD, MSc; Cyrus Desouza, MBBS; Pierre Gourdy, MD, PhD; Soumitra Kar, MSc; André Vianna, MD, PhD; Tina Vilsbøll, MD, DMsc; Siri Vinther, MD, PhD; Yiming Mu, MD

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



Icodec: maggiore % di pazienti a target dopo 26 settimane

TRIALS

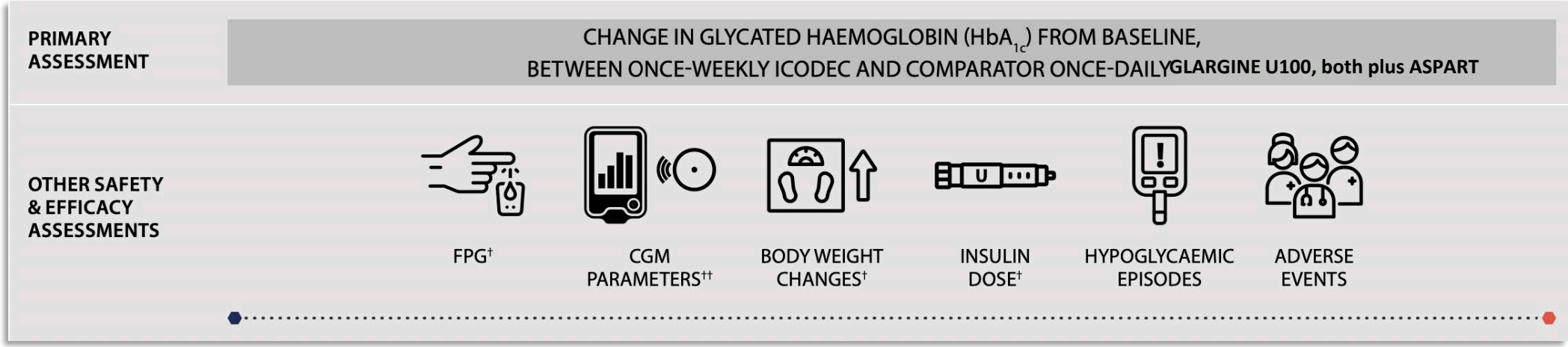
ONWARDS 6

Open-label

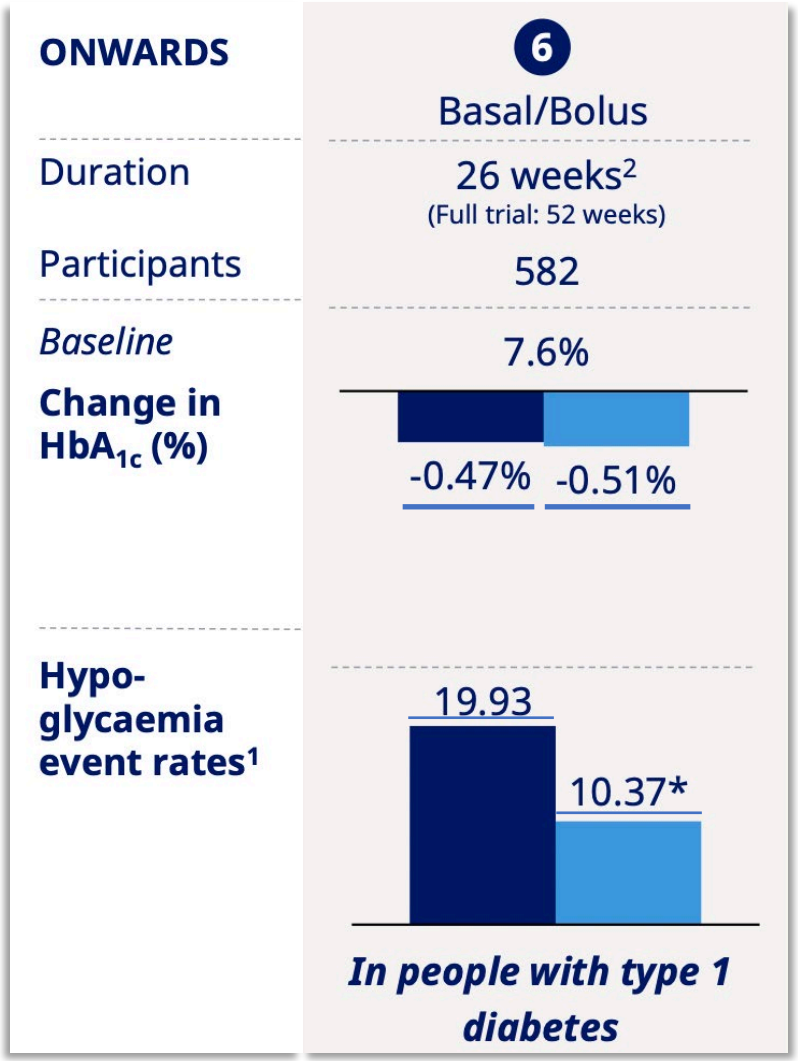
Treat-to-target

580 pazienti **T1D in Basal Bolus**, ≥ 18 anni

52 settimane



ONWARDS-6



✓ **Non inferiorità** in **riduzione** di **HbA1c**

✗ **Maggior** tasso di **ipoglicemie** di **grado 2 o severe**

What’s next? IcoSema

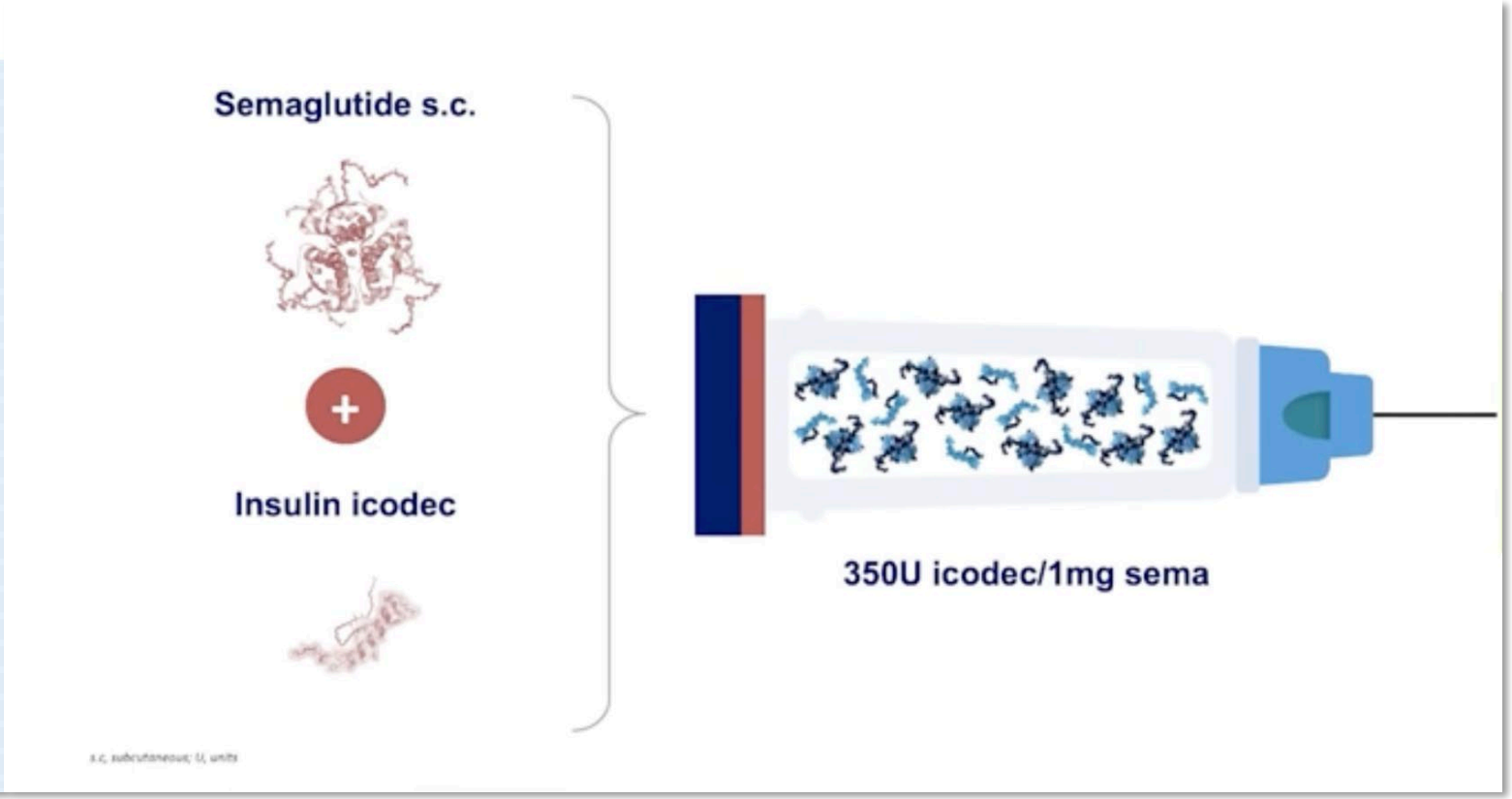
IcoSema characteristics

IcoSema is a fixed dose combination of insulin icodec and semaglutide

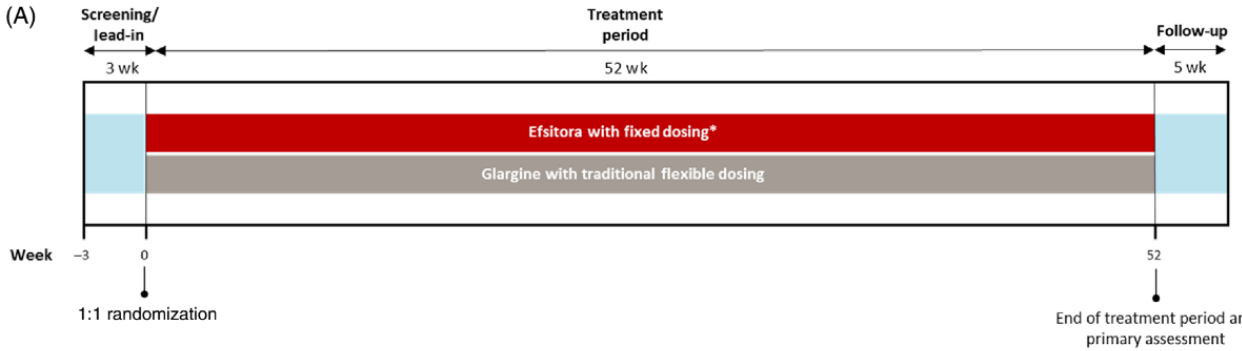
- Simple and convenient once-weekly injection

Phase 3a programme with IcoSema

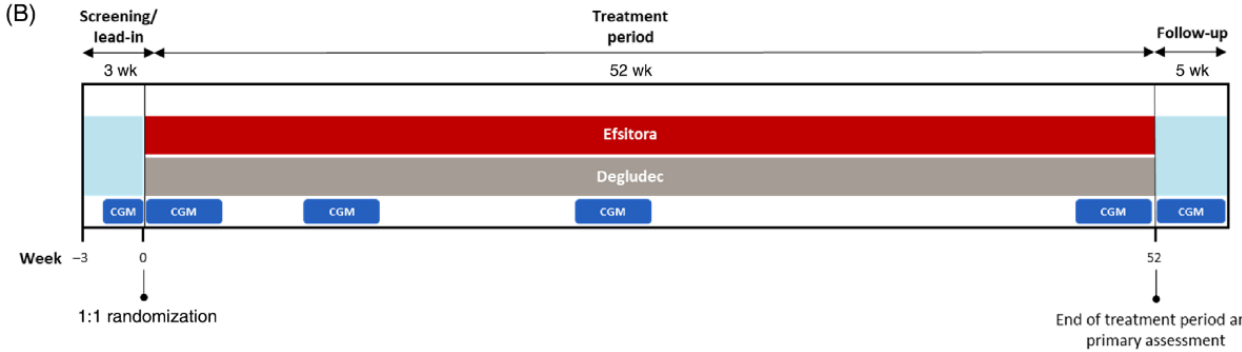
- Aims to confirm efficacy and safety across three global trials
- Expected completion during 2024

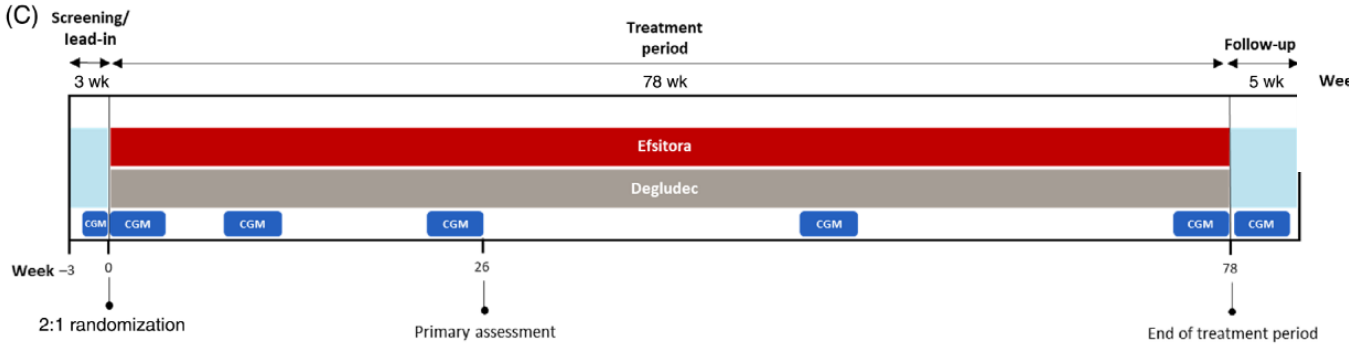


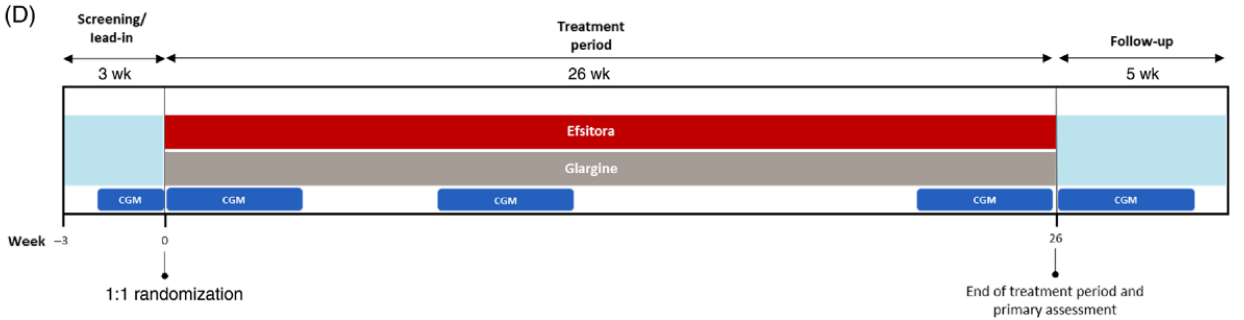
Efsitora Alfa: QWINT Program

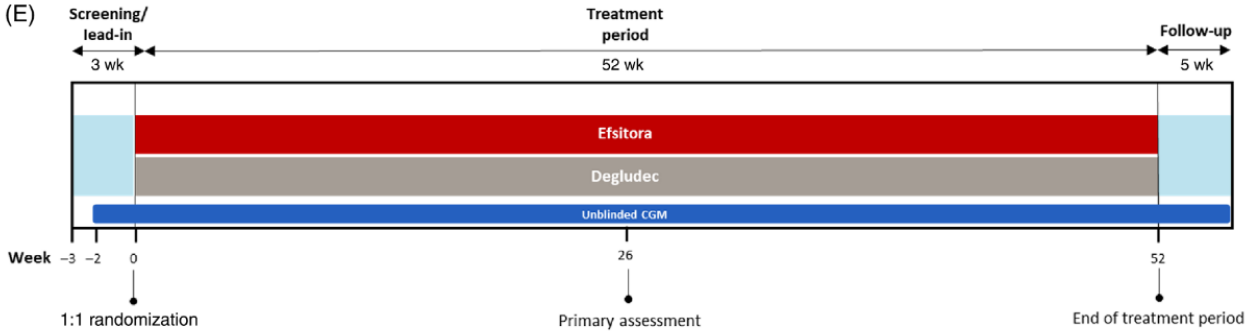


*Participants start with 100 U/week then titrate up to next dose (150 then 250 then 400 U/week) every 4 wk if targets are not met and no hypoglycaemia









Once-weekly insulin efsitora alfa versus once-daily insulin degludec in adults with type 1 diabetes (QWINT-5): a phase 3 randomised non-inferiority trial

Richard M Bergenstal, Ruth S Weinstock, Chantal Mathieu, Yukiko Onishi, Vishali Vijayanagaram, Michelle L Katz, Molly C Carr, Annette M Chang

Summary

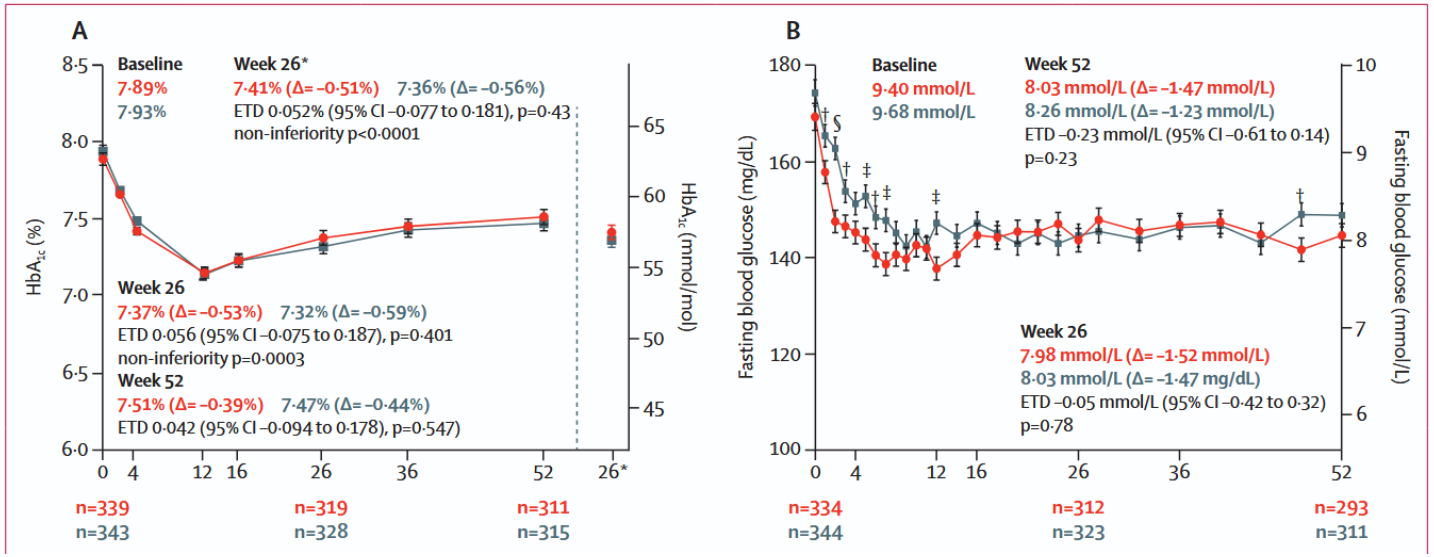
Background Insulin efsitora alfa (efsitora) is a once-weekly basal insulin. This phase 3 study aimed to assess the efficacy and safety of efsitora compared with insulin degludec (degludec) in adults with type 1 diabetes.

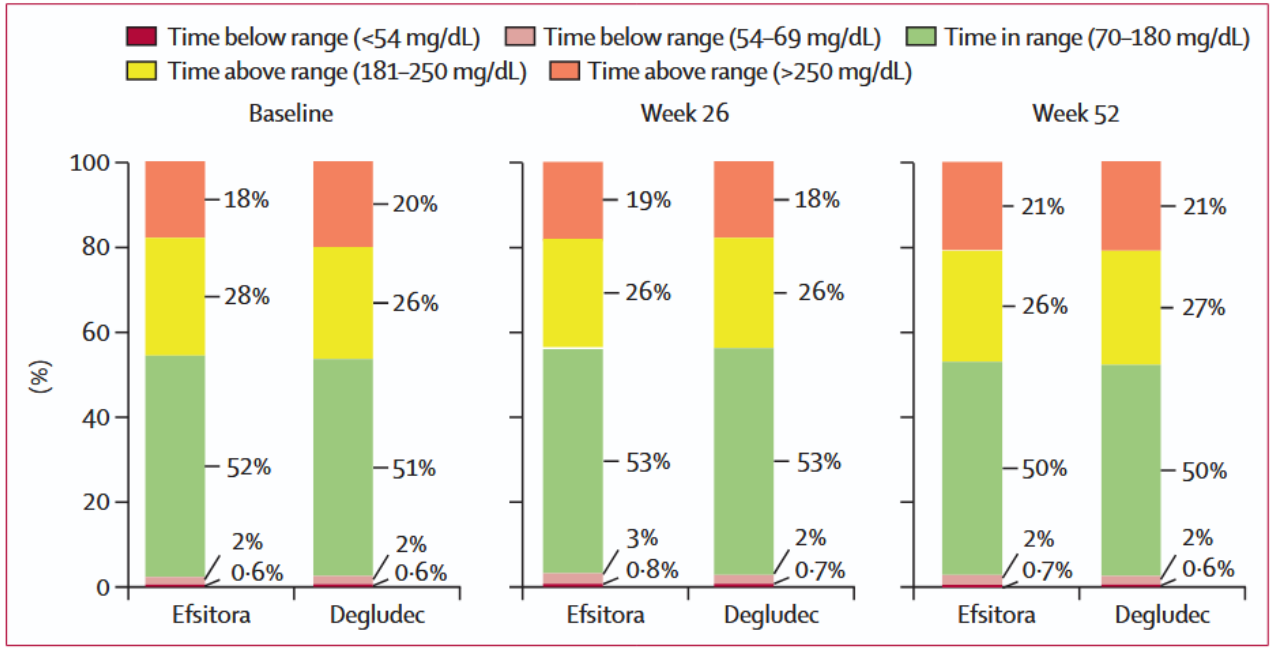
Methods This randomised, 52-week, parallel-design, open-label, treat-to-target non-inferiority study conducted at 82 global health-care centres, randomly assigned (1:1) adults (ie, those aged ≥18 years) with type 1 diabetes glycated haemoglobin A_{1c} (HbA_{1c}) 7·0–10·0% (53·0–85·8 mmol/mol) to efsitora (n=343) or, degludec (n=349), both in combination with insulin lispro. The primary endpoint was the change in HbA_{1c} from baseline to week-26 (non-inferiority margin=0·4%). The trial was registered at ClinicalTrials.gov (NCT05463744) and is completed.

Findings Between Aug 12, 2022, and May 7, 2024, of 893 participants enrolled, 692 (77%) participants were randomly assigned to once-weekly efsitora or once-daily degludec, and 623 (90%) participants completed the study. Mean HbA_{1c} decreased from 7·88% (62·66 mmol/mol) at baseline to 7·41% (57·5 mmol/mol) at week 26 with efsitora and from 7·94% (63·3 mmol/mol) at baseline to 7·36% (56·9 mmol/mol) at week 26 with degludec. Mean HbA_{1c} change from baseline to week 26 was –0·51% with efsitora and –0·56% with degludec (estimated treatment difference 0·052%, 95% CI –0·077 to 0·181; p=0·43), confirming a non-inferiority margin of 0·4% for efsitora compared with degludec. Rates of combined level 2 (<54 mg/dL [3·0 mmol/L]) or level 3 severe hypoglycaemia were higher with efsitora compared with degludec (14·03 *vs* 11·59 events per patient year of exposure; estimated rate ratio 1·21, 95% CI 1·04 to 1·41; p=0·016) during weeks 0–52, with the highest rates during weeks 0–12. Severe hypoglycaemia incidence was higher with efsitora (35 [10%] of 343) versus degludec (11 [3%] of 349) during weeks 0–52. Overall incidence of treatment-emergent adverse events was similar across treatment groups. One death not related to the study treatment occurred in the degludec group.

Interpretation In adults with type 1 diabetes, once-weekly efsitora showed non-inferior HbA_{1c} reduction compared with daily insulin degludec. Higher rates of combined level 2 or level 3 hypoglycaemia and greater incidence of severe hypoglycaemia in participants treated with efsitora compared with participants treated with degludec might suggest the need for additional evaluation of efsitora dose initiation and optimisation in people with type 1 diabetes.

	Efsitora (n=343)		Degludec (n=349)		Efsitora *vs* Degludec
	Participants, n (%)	Episodes (rate per patient-year exposure)	Participants, n (%)	Episodes (rate per patient-year exposure)	Estimated relative rate (95% CI); p value
Hypoglycaemic episodes (overall)					
Level 1 hypoglycaemia					
Week 0–26	339 (99%)	7474 (46·04)	333 (95%)	6586 (39·13)	1·18 (1·05–1·32); p=0·0055
Week 0–52	340 (99%)	12 299 (39·19)	337 (97%)	11 122 (33·99)	1·15 (1·03–1·29); p=0·016
Combined level 2 or level 3 severe hypoglycaemia					
Week 0–26	293 (85%)	2662 (17·19)	289 (83%)	2319 (14·06)	1·22 (1·04–1·43); p=0·013
Week 0–52	305 (89%)	4175 (14·03)	306 (88%)	3740 (11·59)	1·21 (1·04–1·41); p=0·016
Level 3 severe hypoglycaemia					
Week 0–26	28 (8%)	35 (0·21)	9 (3%)	11 (0·06)	3·23 (1·42–7·38); p=0·0052
Week 0–52	35 (10%)	44 (0·14)	11 (3%)	13 (0·04)	3·44 (1·64–7·19); p=0·0011





Bergenstal RM et al. Lancet 2024;404:1132-42

Conclusioni

Le nuove insuline ultrarapide

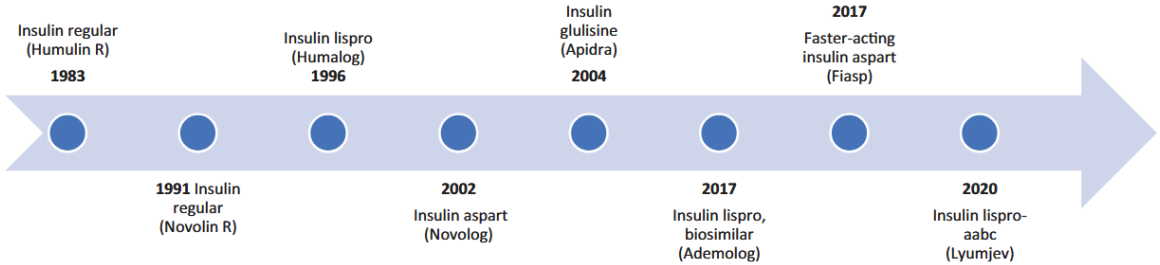
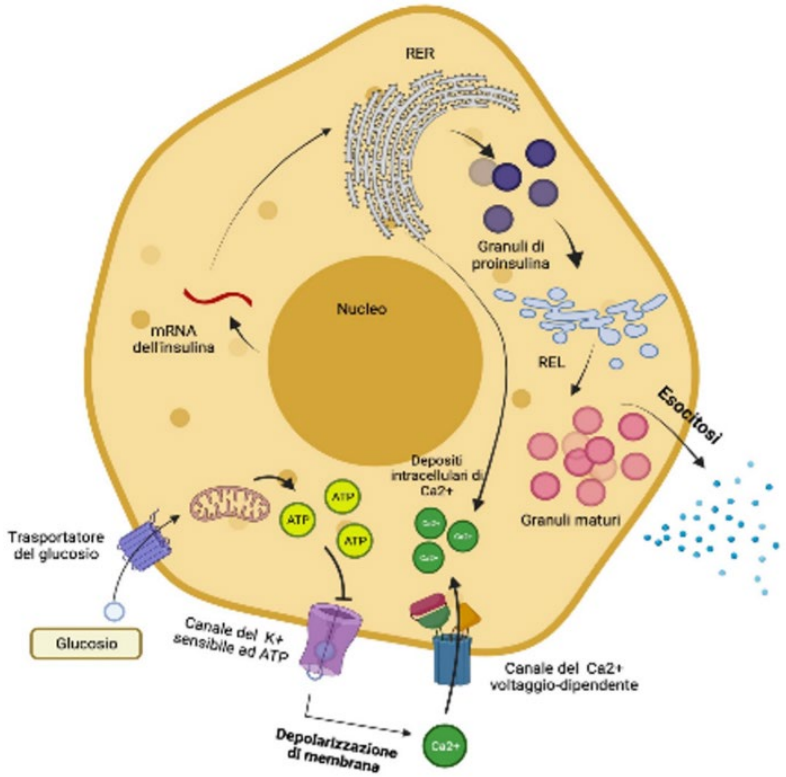
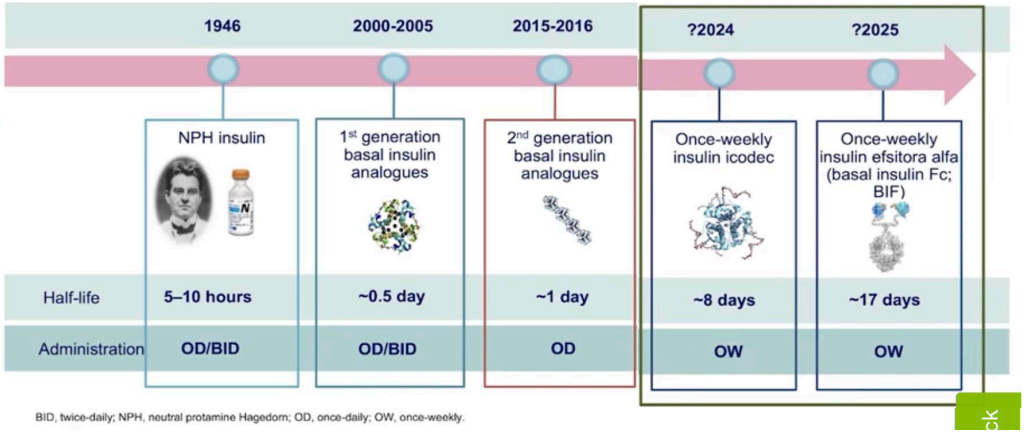


FIGURE 1 Timeline of U.S. Food and Drug Administration approval of bolus insulins (6).



Le nuove insuline ultralente



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

Grazie per l’attenzione