CONGRESSO REGIONALE SID-AMD
"UMBRIA DIABETE 2024 RITORNO AL FUTURO"

INSULINA SETTIMANALE

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23 NOVEMBRE 2024

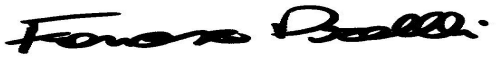
Disclosure

La sottoscritta Dr.ssa Francesca Porcellati dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abbott
- Astra Zeneca
- Eli-Lilly
- Laboratori Guidotti
- 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.).

In fede, Francesca Porcellati



Ever-increasing insulin-requiring people globally

537 million
people with diabetes in the world (2021)

783 million
people with diabetes in the world (2045)

Despite tremendous advantages in pharmacological options, basal insulin continues to be a vital part of therapy for many persons with T2 diabetes

Thirty millions are persons with T1D

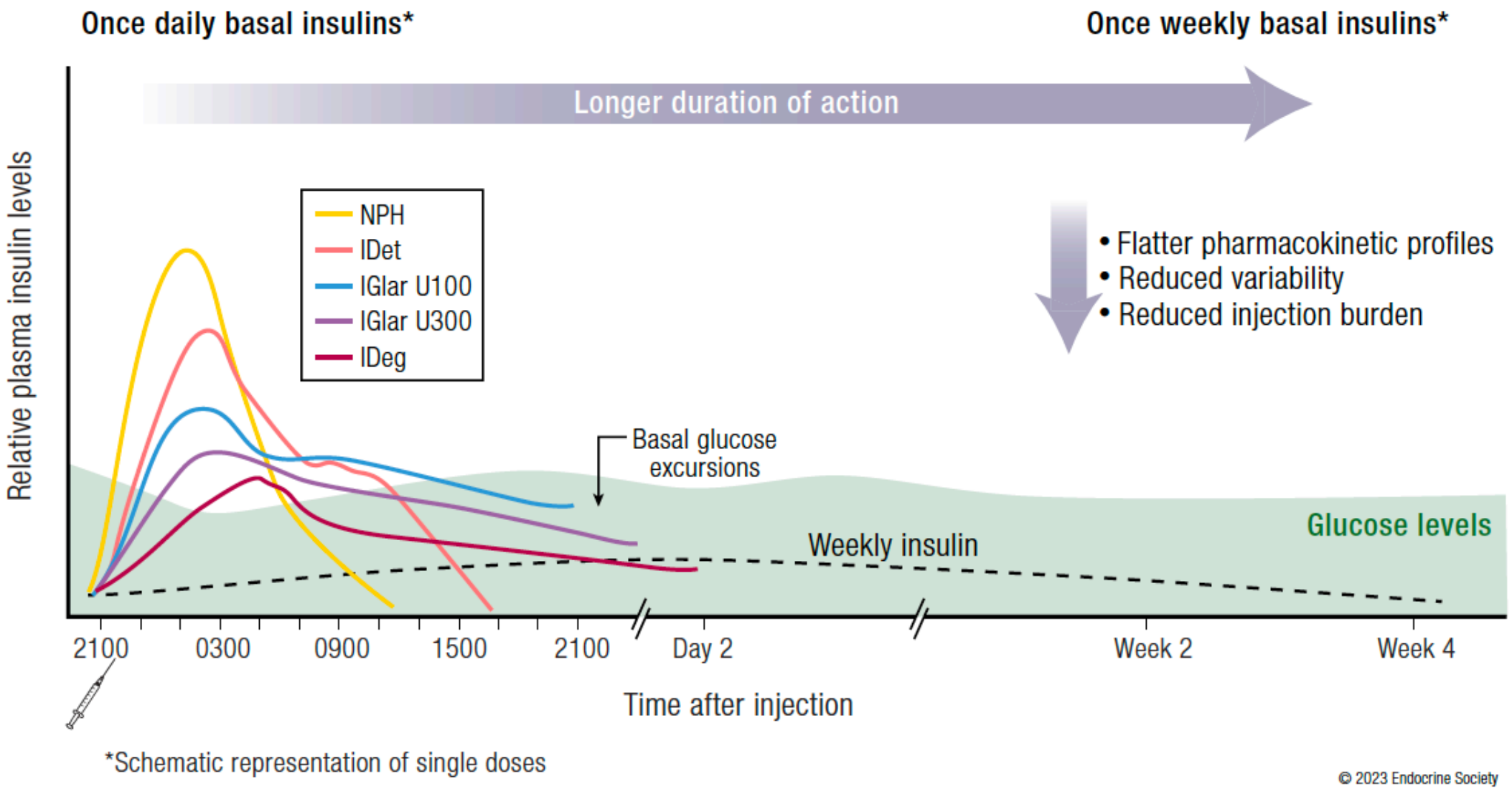
10%–20% of persons with T2D are antibody positive.

require insulin during the course of T2D

Cumulatively we have about 150– 200 million people requiring insulin therapy worldwide

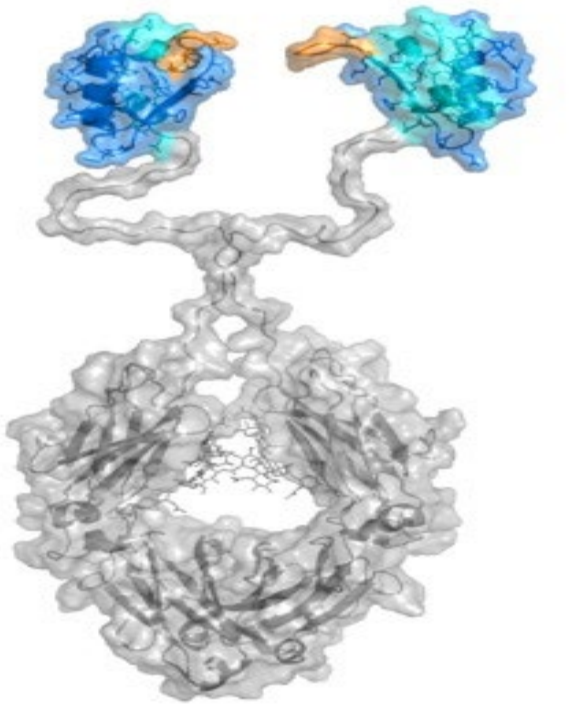
T1D, type 1 diabetes; T2D, type 2 diabetes.
1. Adapted from IDF Diabetes Atlas (10th edition). International Diabetes Federation. 2022. http://www.diabetesatlas.org/. Accessed January 2024.

The Need to Achieve a Favorable Insulin-action Profile



Currently Explored Technologic Approaches to Increase Half-life of Basal Insulin

Insulin BIF (insulin efsitora alfa)



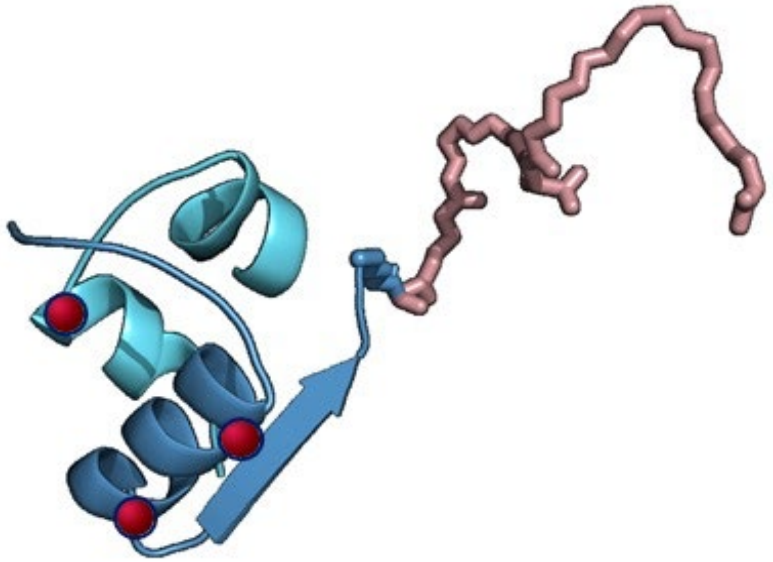
Novel single-chain variant of insulin fused to human IgG Fc domain Homo-dimer

Reduced insulin receptor potency with full agonism

Time-action profile (t½ = approx. 17 days) supports once-weekly dosing in humans[3]

Currently in Phase 3 Trials

Insulin icodec



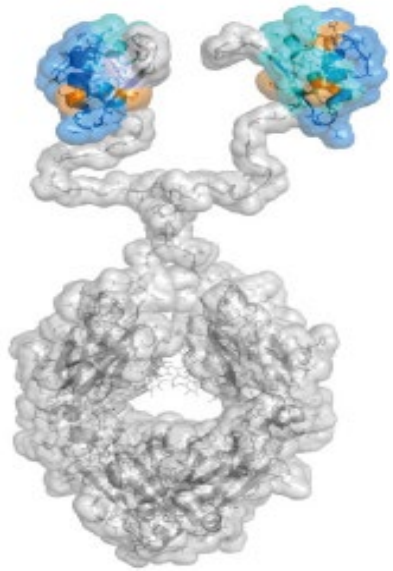
Acylated insulin: 20-carbon fatty diacid sidechain High albumin binding

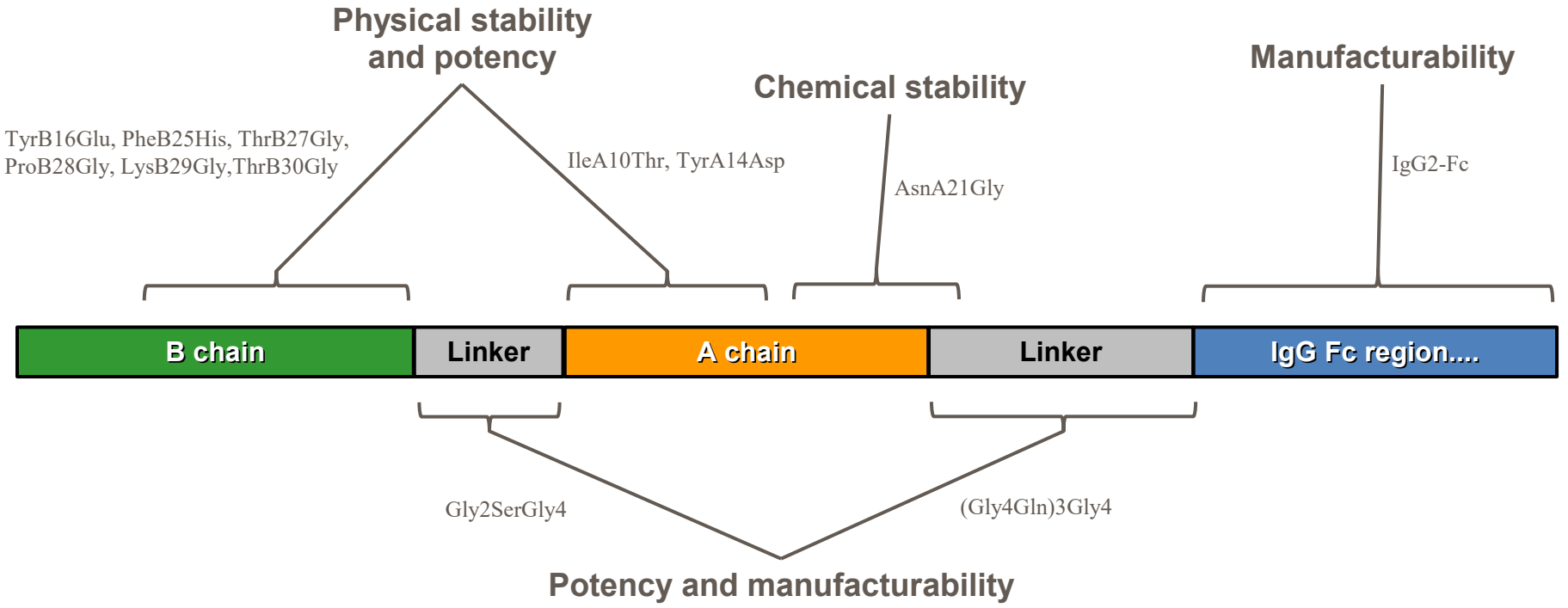
Reduced enzymatic degradation Reduced insulin receptor-mediated clearance

Time-action profile (t½ = approx. 8 days) supports once-weekly dosing in humans

Planned 5 trials of Phase 3 have been concluded

Currently Explored Technologic Approaches to Increase Half-life of Basal Insulin: Basal Insulin Fc (BIF)[1]

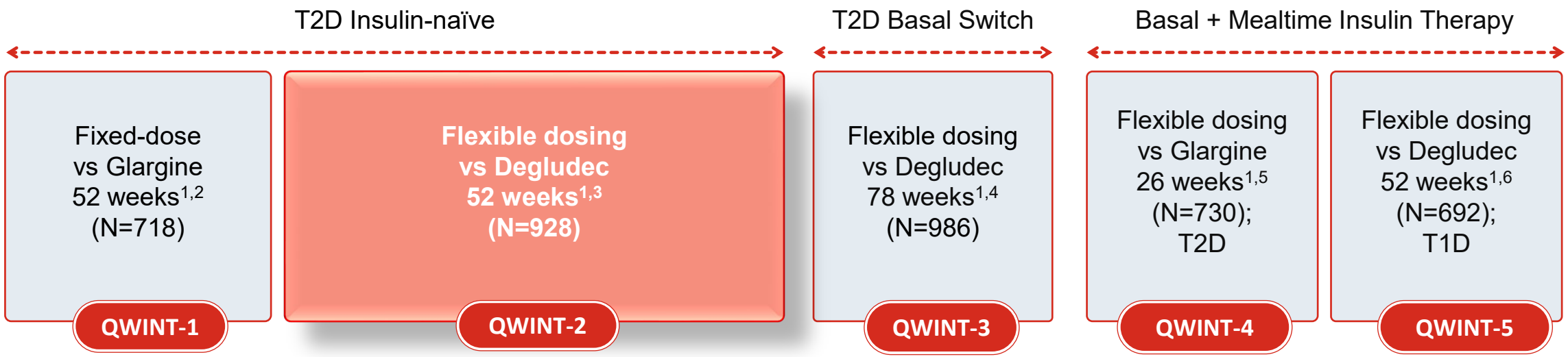




1. Heise T et al. Basal Insulin Fc (BIF), A Novel Insulin Suited For Once Weekly Dosing For The Treatment of Patients With Diabetes Mellitus, Journal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021, Page A329, https://doi.org/10.1210/jendso/bvab048.672.

QWINT: Once-weekly Insulin Efsitora Alfa

Open-label, treat-to-target studies designed to achieve non-inferior glycemic control to daily basal insulins.



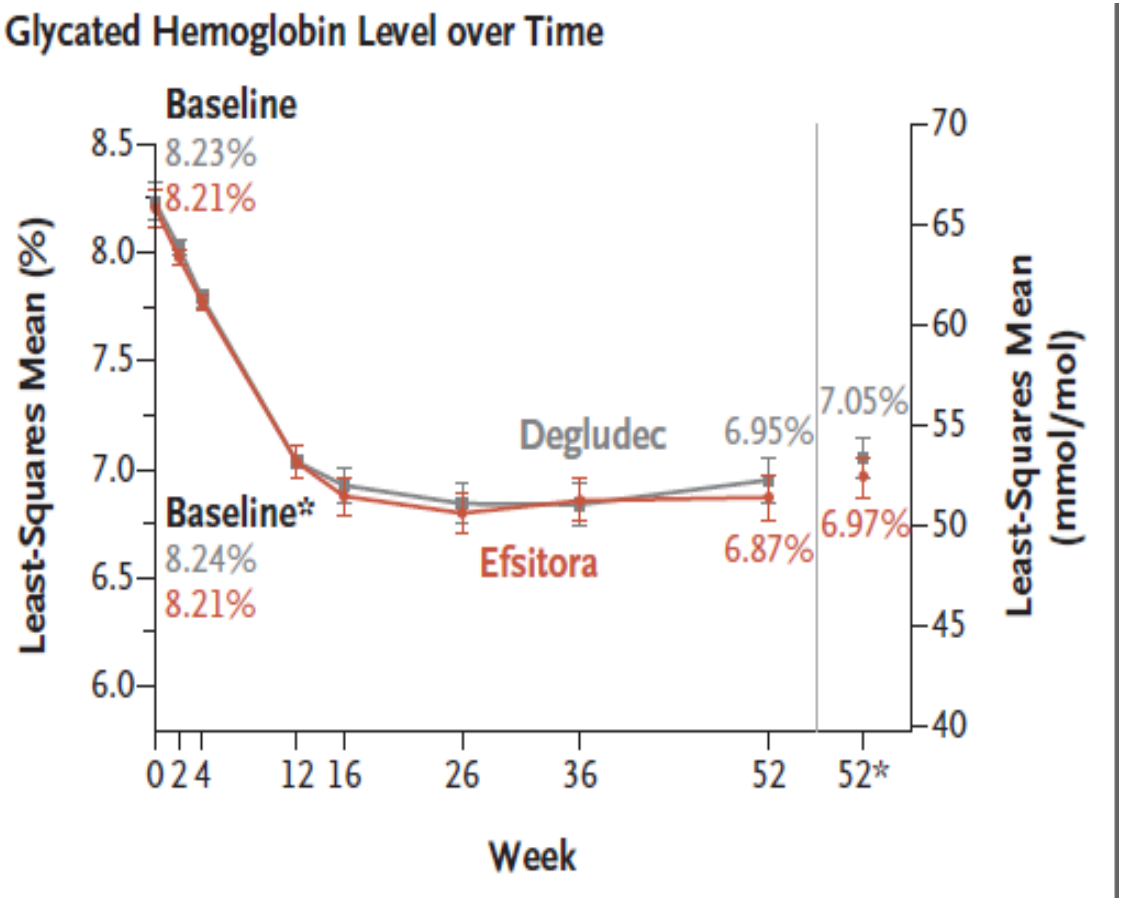
- N=Targeted Sample Size; QWINT=Once-Weekly Insulin Therapy; T1D=Type 1 Diabetes; T2D=Type 2 Diabetes.
- 1. Bergenstal RM, et al. *Diabetes Obes Metab.* 2024;26(8):3020-3030. 2. https://clinicaltrials.gov/ct2/show/NCT05662332 (Accessed July 30, 2024). 3. https://clinicaltrials.gov/ct2/show/study/NCT05362058 (Accessed July 30, 2024). 4. https://clinicaltrials.gov/ct2/show/study/NCT05275400 (Accessed July 30, 2024). 5. https://clinicaltrials.gov/ct2/show/NCT05462756 (Accessed July 30, 2024).
- 6. https://clinicaltrials.gov/ct2/show/NCT05463744 (Accessed July 30, 2024).

QWINT: Once-weekly Insulin Efsitora Alfa

T2D Insulin-naïve

Flexible dosing
vs Degludec
52 weeks[1,3]
(N=928)

QWINT-2



Wysham C, et al. *NEJM.* 2024;doi:10.1056/NEJMoa2403953 (Ahead of print).

Qwint 2: Conclusion

Efsitora demonstrated noninferiority to once-daily degludec in reducing HbA1c levels over 52 weeks in insulin-naïve adults with T2D

Efsitora was non-inferior to degludec in HbA1c change for participants with or without GLP-1 RAs. Hypoglycemia rates were low among GLP-1 RA users demonstrating Efsitora can be effectively and safely added to such therapy

Efsitora led to low rates of clinically significant hypoglycemia, less than one event per year, and was not associated with severe hypoglycemia

Efsitora led to a clinically meaningful increase and numerically higher TIR (70-180 mg/dL) with similar TBR (<54 mg/dl) compared to degludec

Change in BW was similar between treatment groups, and consistent with weight gain associated with improvement of glycemic control with insulin therapy

Efsitora demonstrated acceptable tolerability, and the safety profile is consistent with expectations for a basal insulin

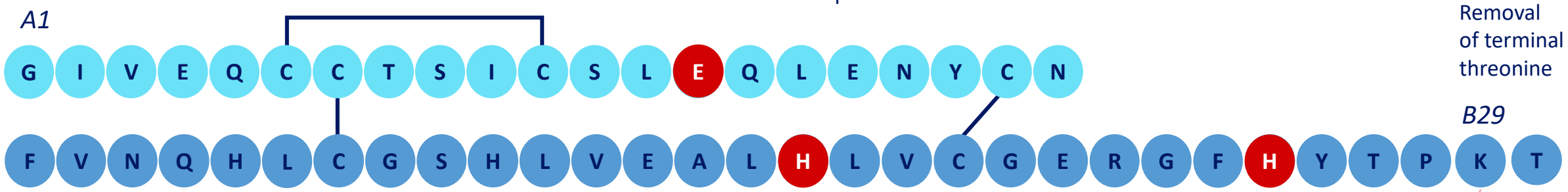
- BW=Body Weight; GLP-1 RA=Glucagon-Like Peptide-1 Receptor Agonists; HbA1c=Glycated Hemoglobin; T2D=Type 2 Diabetes; TIR=Time in Range.
- Wysham C, et al. *NEJM.* 2024;doi:10.1056/NEJMoa2403953 (Ahead of print).

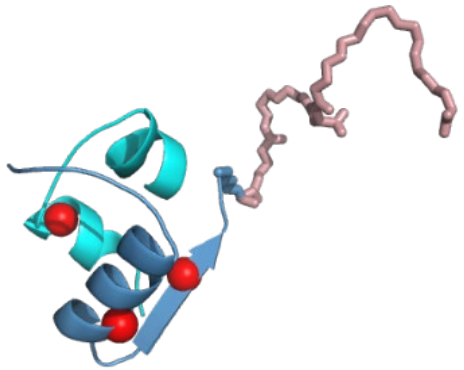
Insulin Icodec

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

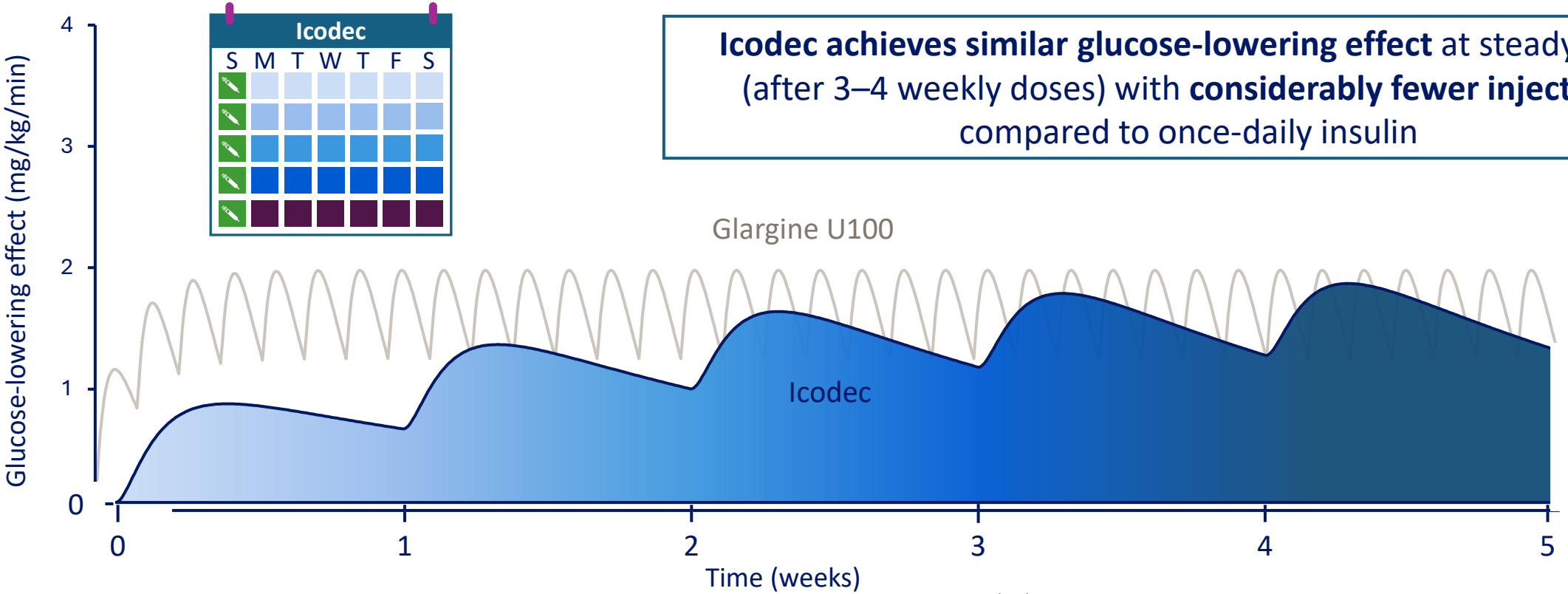
- Strong, reversible binding to albumin
- Reduced receptor-mediated clearance

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

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

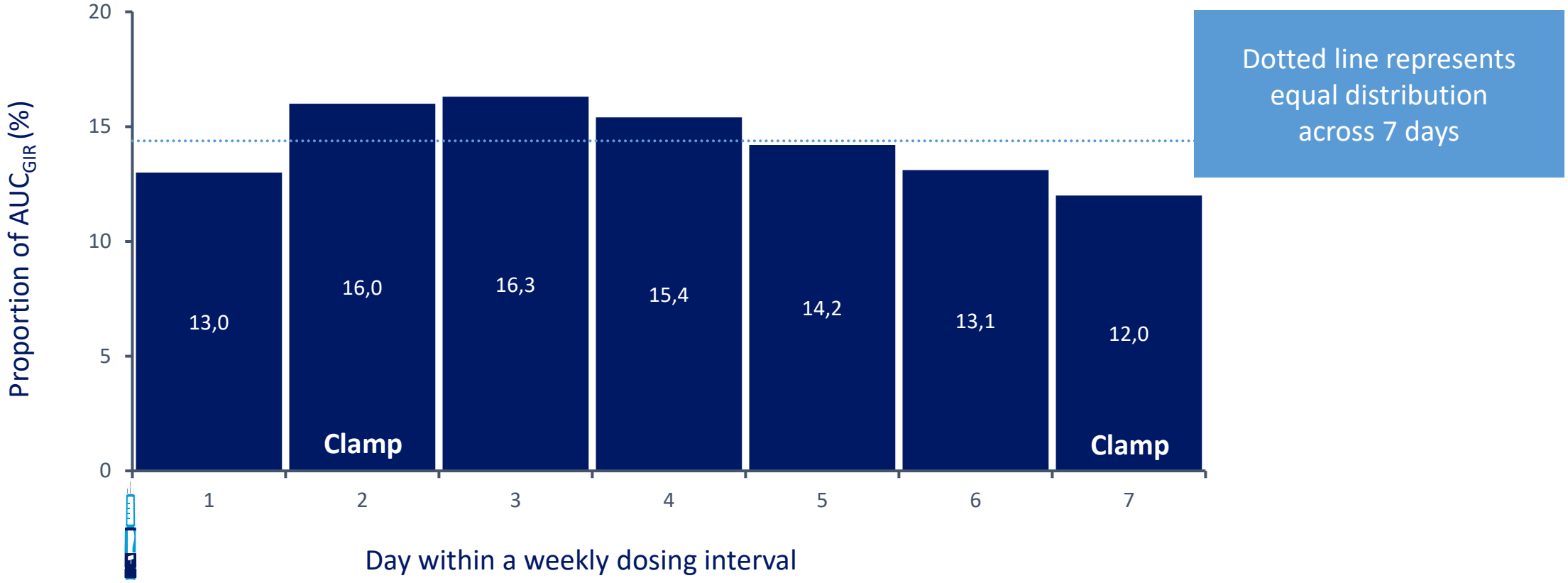


Icodec achieves similar glucose-lowering effect at steady state (after 3–4 weekly doses) with **considerably fewer injections** compared to once-daily insulin

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.

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).

Overview of the ONWARDS programme

Six phase 3 clinical trials

Insulin-naive T2D

ONWARDS 1

Physician survey | CGM

Insulin naïve T2D, N=970, 78 weeks

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

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

ONWARDS 3

Insulin naïve T2D, N=580, 26 weeks

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

Primary endpoint: HbA_{1c} non-inferiority

ONWARDS 5

Patient interview | PRO

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

- Icodec with DoseGuide
- OD basal insulin analogues

Primary endpoint: HbA_{1c} non-inferiority

Insulin-treated T2D

ONWARDS 2

PRO | CGM | Patient interview

Basal switch T2D, N=520, 26 weeks

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

Primary endpoint: HbA_{1c} non-inferiority

ONWARDS 4

CGM

Basal-bolus T2D, N=580, 26 weeks

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

Primary endpoint: HbA_{1c} non-inferiority

Insulin-treated T1D

ONWARDS 6

PRO | CGM

Basal-bolus T1D, N=580, 52 weeks

- Icodec + IAsp
- IDeg + IAsp

Primary endpoint: HbA_{1c} non-inferiority

HbA_{1c}, glycated 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

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

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

Baseline Characteristics

	Total (N = 984)
Sex, Male (%)	56.7
Age (years)[a]	59.0 ± 9.9
Diabetes Duration (years)[a]	11.5 ± 6.7
A1C (%)[a]	8.5 ± 1.0
A1C (mmol/mol)	69.1 ± 11.0
FPG (mmol/L)[a]	10.3 ± 2.8
FPG (mg/dL)[a]	186 ± 50
Body Weight (kg)[a]	84.7 ± 17.7
BMI (kg/m^2)	30.1 ± 4.9

Baseline Glucose-Lowering Agents

	Total (N = 984)	
	n	**%**
Metformin	885	89.9
SU	446	45.3
SGLT2i	359	36.5
DPP-4i	348	35.4
GLP-1RA	175	17.8
Thiazolidinediones	49	5.0
Alpha-glucosidase inhibitor	45	4.6
Glinides	26	2.6

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

Titration Algorithm for Basal Insulins

Pre-Breakfast SMBG		Glargine U100 Daily Dose Adjustments	Icodec Weekly Dose Adjustments
Up-Titra	Mean of the SMBG values	+3 U	+20 U
Target	Mean of the SMBG values in the range 80–130 mg/dL (4.4–7.2 mmol/L)	0 U	0 U
Down-Titration	Lowest SMBG value < 80 mg/dL (< 4.4 mmol/L)	–3 U	–20 U

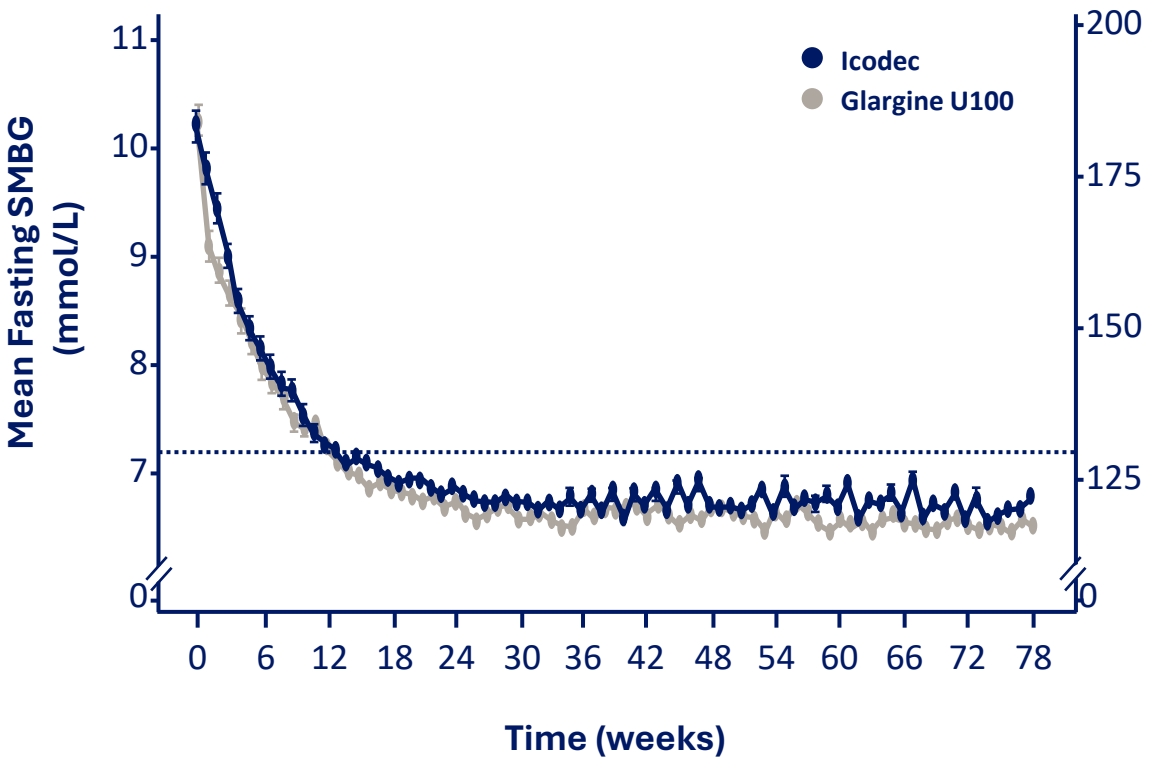
Starting Doses:
Icodec 70 U and Glargine 10 U

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

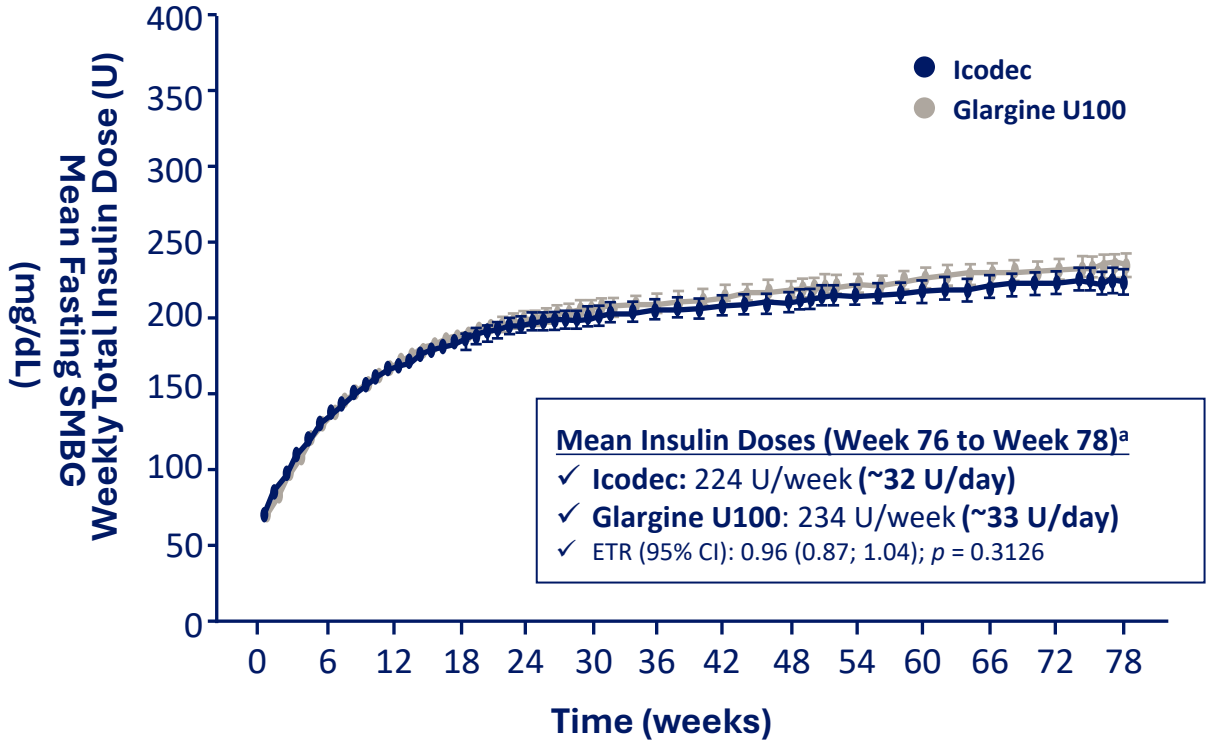
N Engl J Med. 2023 Jul 27;389(4):297-308.

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

Fasting Glucose Over Time from SMPG for Dose Adjustments

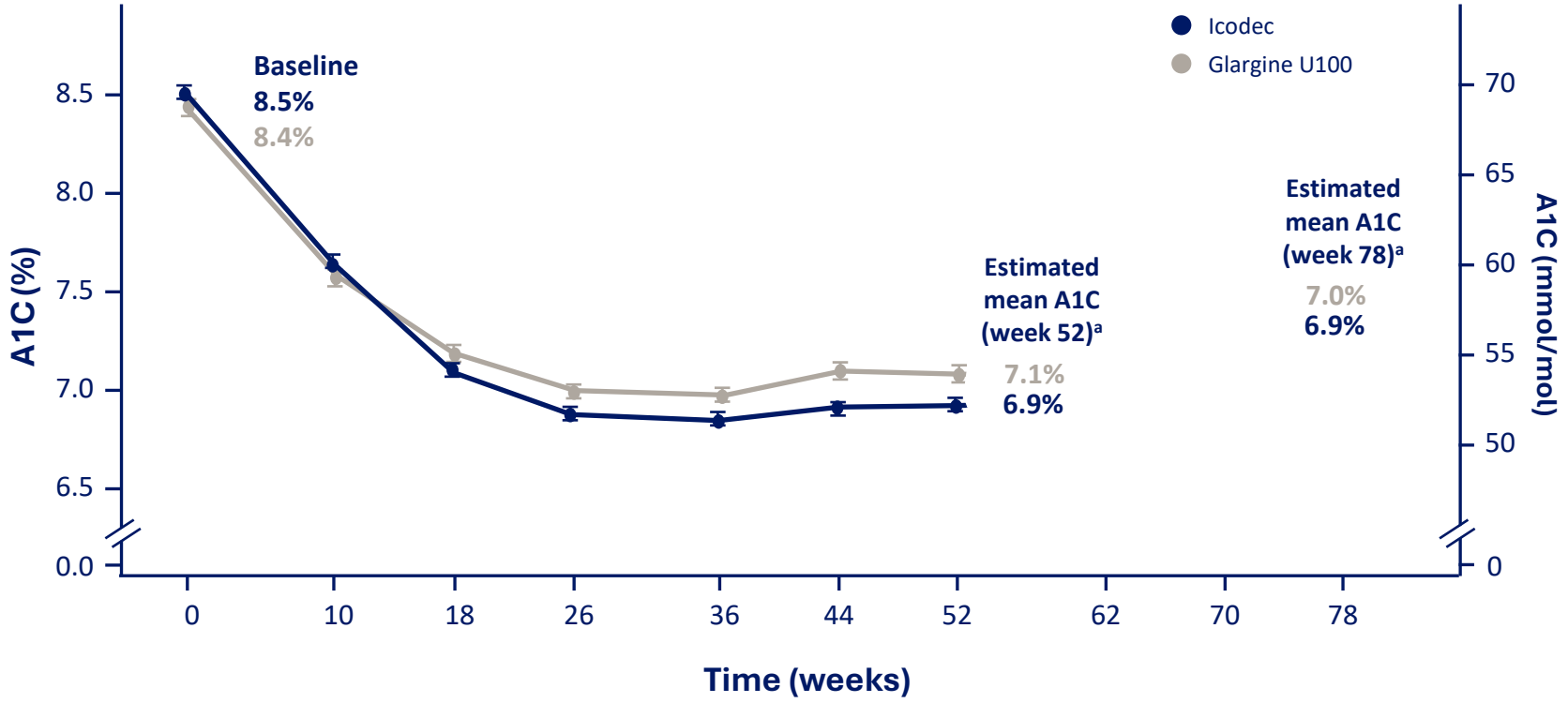


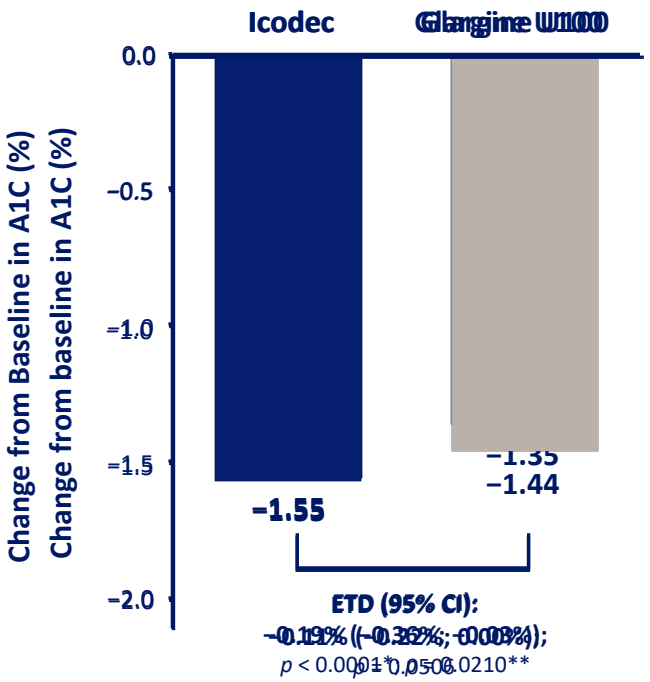
Weekly Total Insulin Doses Over Time



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

A1C Changes Over Time and at Week 52





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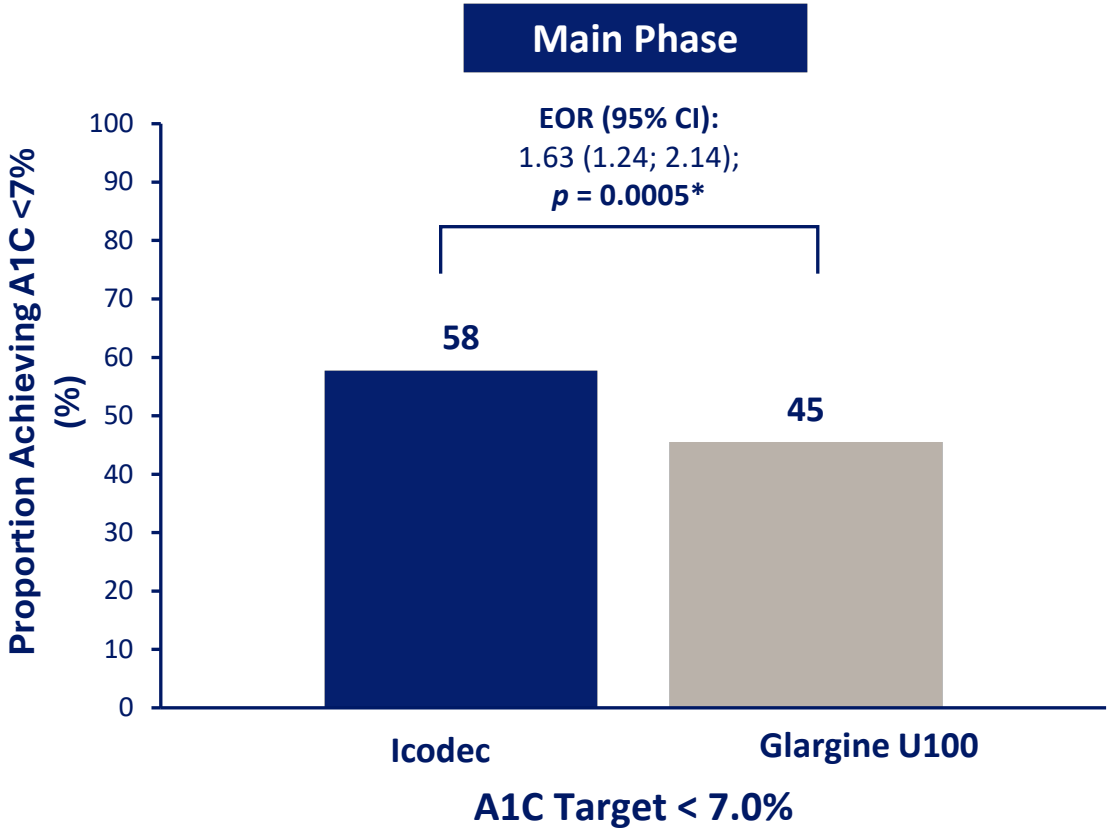
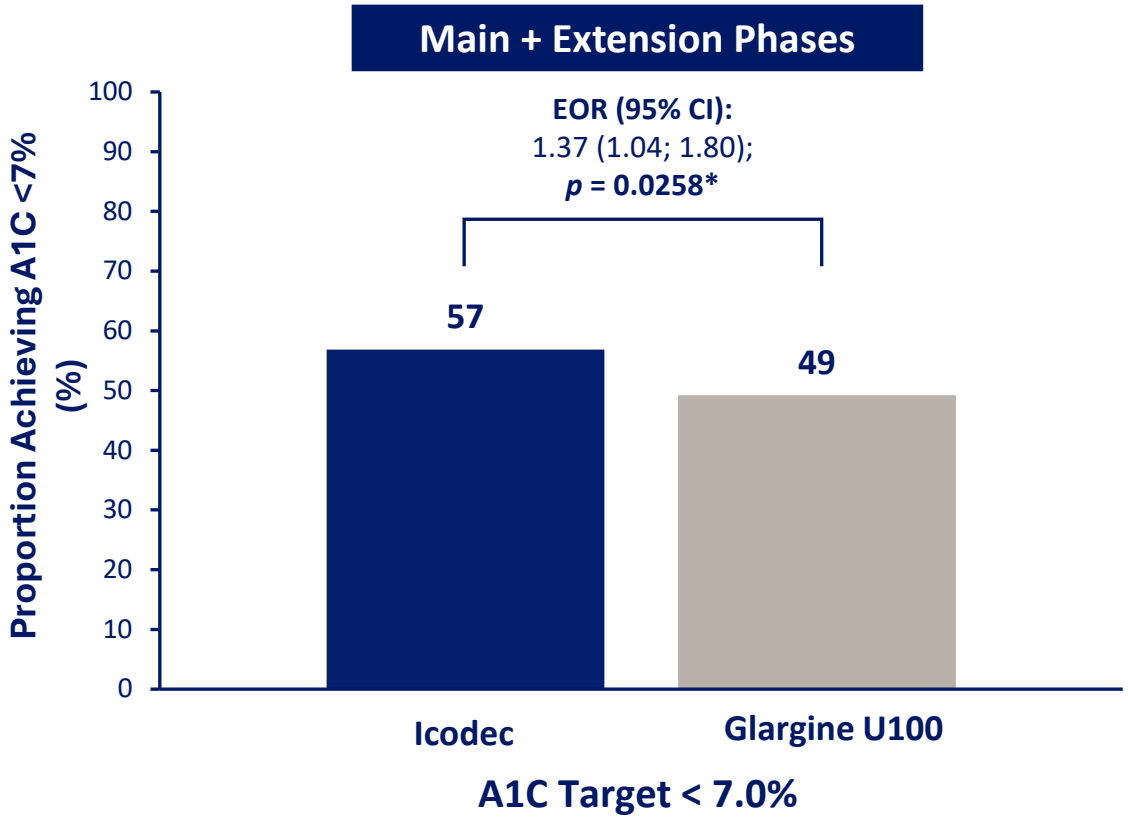
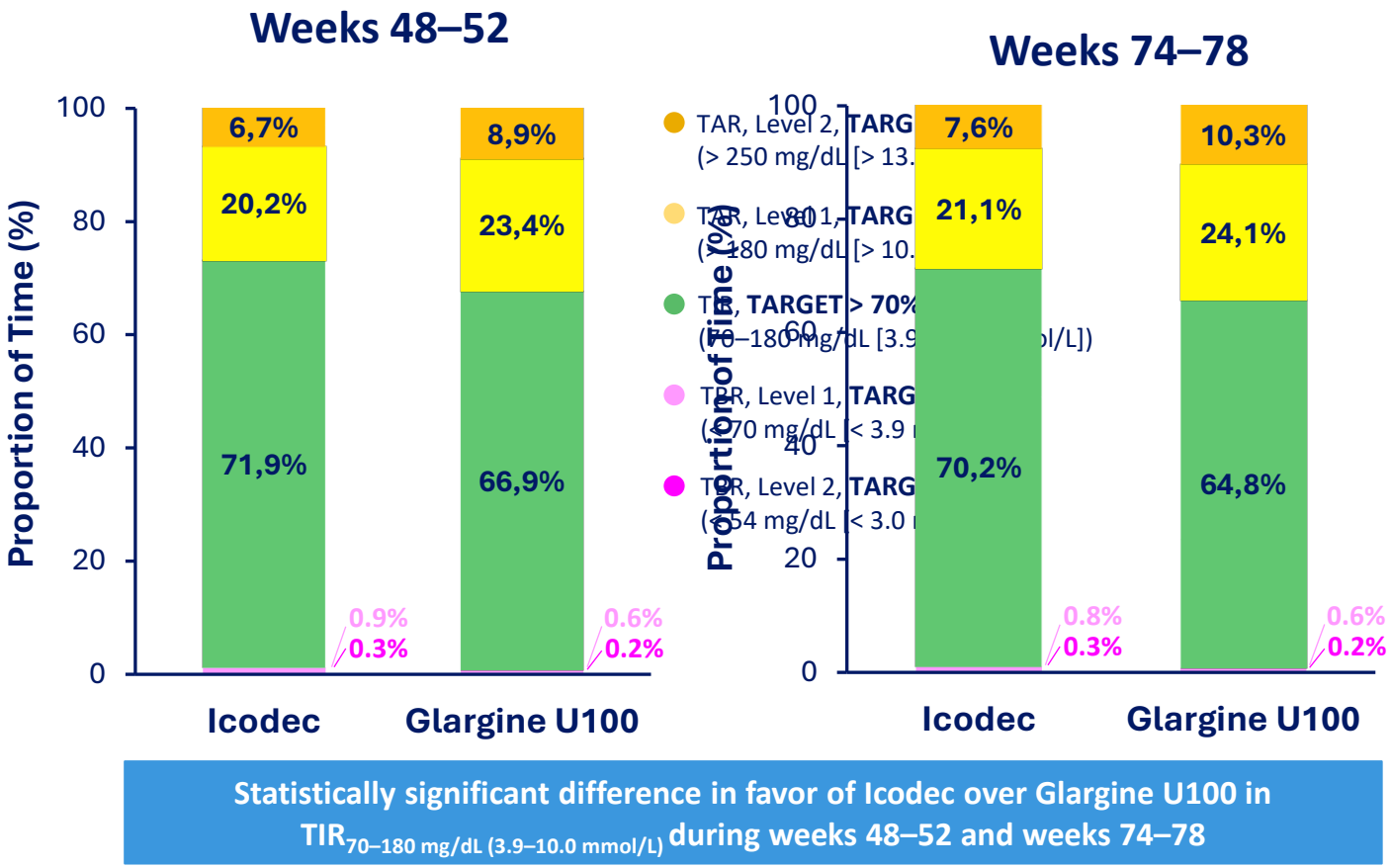
Target A1C <7% Attainments at Week 52





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

CGM Metrics During Weeks 48–52



Statistically significant difference in favor of Icodec over Glargine U100 in $TIR_{70–180\ mg/dL\ (3.9–10.0\ mmol/L)}$ during weeks 48–52 and weeks 74–78

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

Results

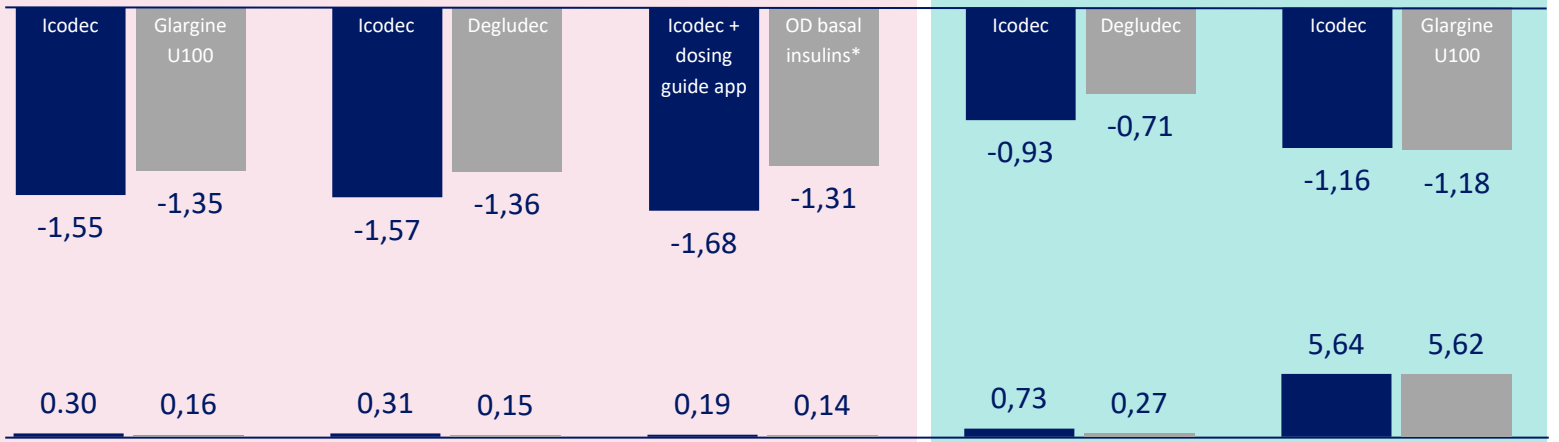
Overall hypoglycemic episodes

- 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)

ONWARDS Programme: Topline Results

	ONWARDS 1 BASAL INITIATION	ONWARDS 3 BASAL INITIATION	ONWARDS 5 BASAL INITIATION	ONWARDS 2 BASAL SWITCH	ONWARDS 4 BASAL/BOLUS SWITCH
Trial duration (weeks)	52 (78)	26	52	26	26
Baseline HbA_{1c}	8.5	8.5	8.9	8.13	8.3
Non-inferiority confirmed	✓	✓	✓	✓	✓
Superiority confirmed	✓	✓	✓	✓	
Endpoint assessed (week)	**52**	**26**	**52**	**26**	**26**



*insulin degludec or insulin glargine U100/U300. 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. OD, once-daily; RCT, randomised clinical trial.

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. EASD 2023 Annual Meeting. OP-09; 8. Russell-Jones D et al. *Lancet*. 2023: DOI: 10.1016/S0140-6736(23)02179-7.