Nouveauté en insulino-thérapie (once weekly Insulins)

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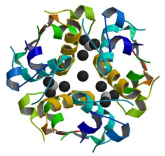
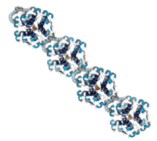
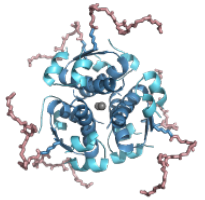
Bruxelles, November 2022

Disclosures

Consultant or speaker for: Abbott, AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Lilly

The past and present of basal insulin innovation

	NPH insulin	1st generation basal insulin analogues	Ultra long-acting basal insulin analogues	Once-weekly icodec
				
Half-life	**5–10 hours**	**~0.5 day**	**~1 day**	**~1 week**
Administration	**OD/BID**	**OD/BID**	**OD**	**OW**

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

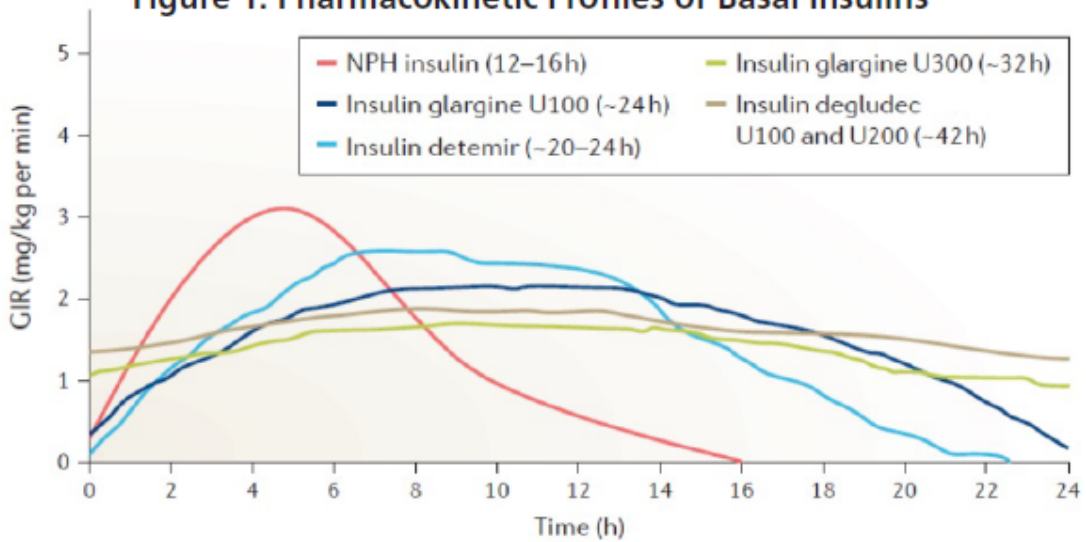
CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

Basal Insulin Analogues: The Next Generation

LMC

Editor
Dr. A. Abitbol
Assistant Medical Director

Figure 1: Pharmacokinetic Profiles of Basal Insulins



Pharmacodynamic Action Profiles of Long-Acting Insulins

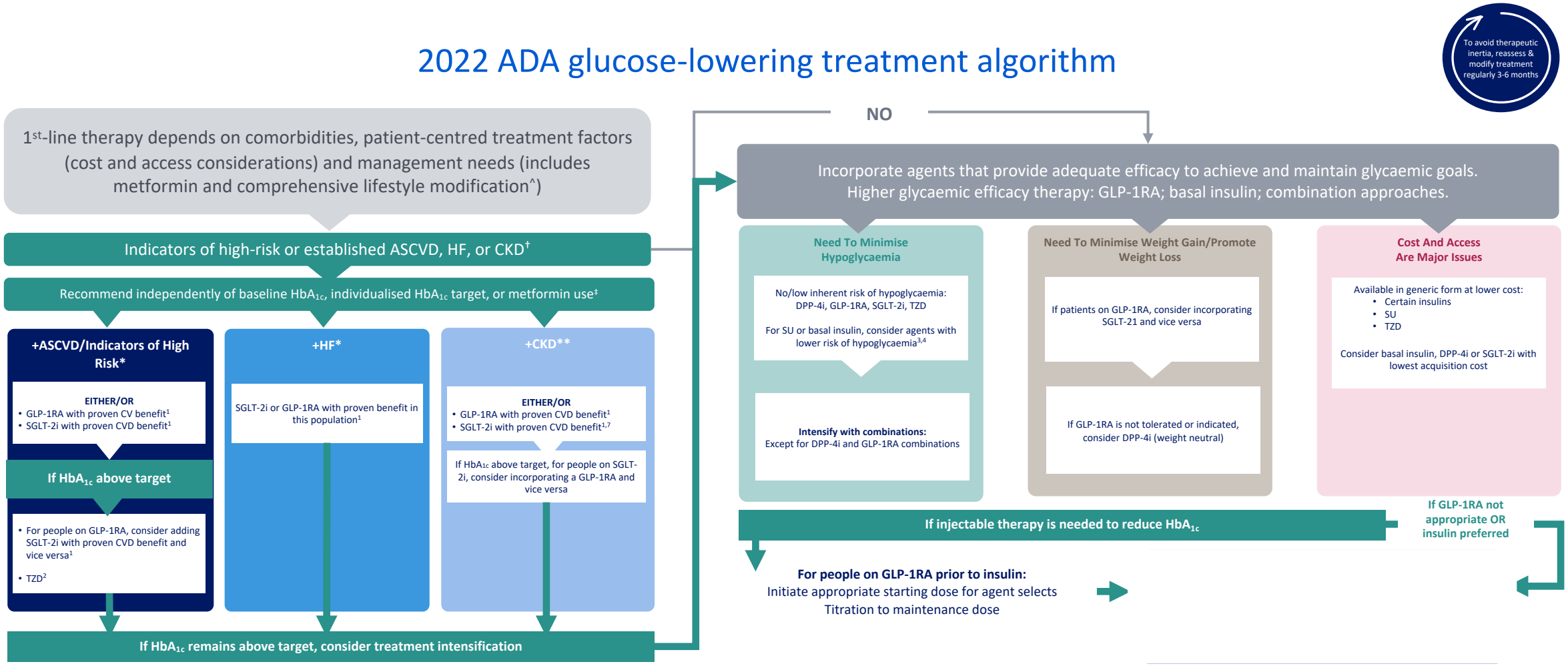
Source: Mathieu, Chantal; Gillard, Pieter; Benhalima, Katrien. Insulin analogues in type 1 diabetes mellitus: getting better all the time. Nature Reviews Endocrinology 2017/04/21/online http://dx.doi.org/10.1038/nrendo.2017.39 (Used with permission)

With this wealth of evidence, one can confidently conclude that the second-generation basal insulin analogues are superior in causing less hypoglycemia.

This head-to-head trial comparing Gla-300 and IDeg in insulin-naïve patients with type 2 diabetes demonstrated that the insulins have more similarities than differences

Basal insulin recommended as the initial insulin option for treatment intensification in T2D

2022 ADA glucose-lowering treatment algorithm



^For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate-to-vigorous physical activity is recommended. †Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications. ‡Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy. *Refer to Section 10: Cardiovascular Disease and Risk Management. **Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria.

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

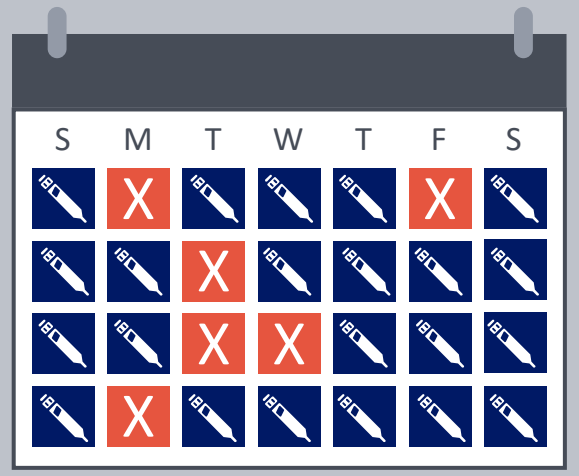
1. Proven benefit refers to label indication, 2. Low dose may be better tolerated though less well studied for CVD benefits, 3. Choose later generation SU to lower risk of hypoglycaemia, 4. Risk of hypoglycaemia: degludec/glargine U-300 < glargine U-100/detemir < NPH insulin, 5. Consider country and region-specific cost of drugs.

Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies et al. and Buse et al. http://diabetesjournals.org/care/article-pdf/45/Supplement_1/S125/635941/dc22s009.pdf.

Barriers to treatment intensification with insulin therapy

Hypoglycaemia

Complexity



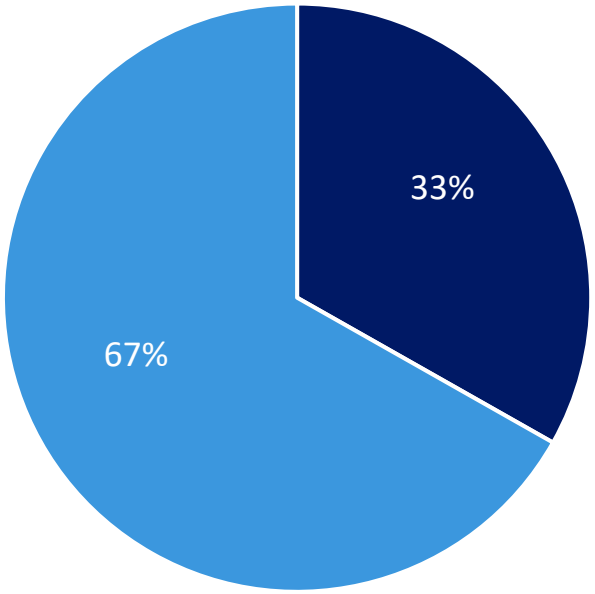
Poor treatment adherence

1. Peyrot M et al. *Diabet Med*. 2012;29(5):682–689.

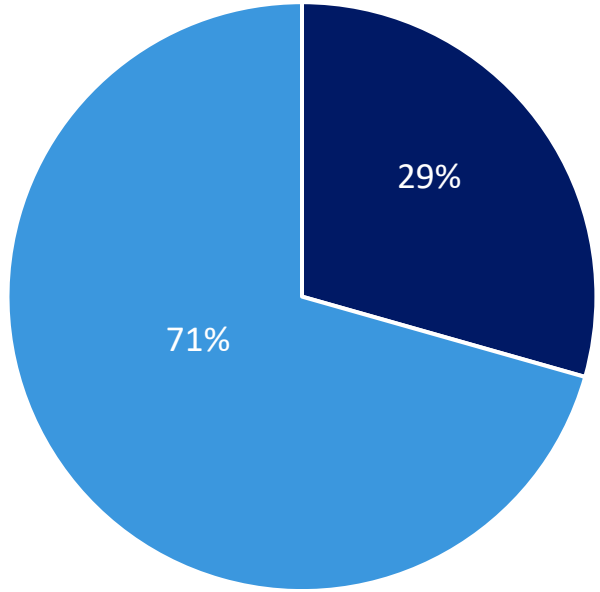
Approximately one-third of people with diabetes are poorly adherent to insulin therapy

Adherent
Poorly adherent

Proportion of people with diabetes reporting poor adherence* to insulin (Multinational study)[1]



Proportion of people with T2D reporting poor adherence (PDC <80%) to insulin (United Kingdom)[2]



*Patient reporting insulin omission/non-adherence at least one day in the last month.
PDC, proportion of days covered.
1. Peyrot M et al. *Diabet Med*. 2012;29(5):682–689; 2. Donnelly LA et al. *QJM*. 2007;100(6):345–350.

Poorly controlled diabetes leads to increased risk of developing diabetes-related complications

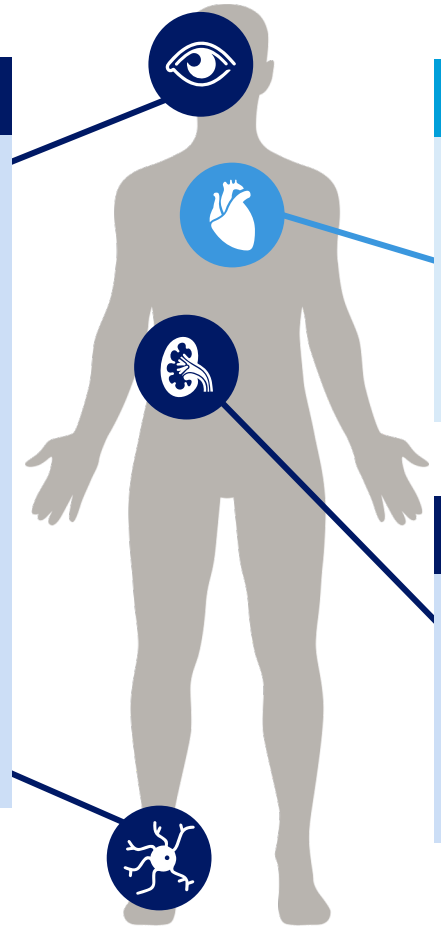
Microvascular

Diabetic retinopathy

- Estimated to affect **35%** of all people with diabetes and is **one of the leading** causes of vision loss in the working age population

Diabetic neuropathy

- Nerve damage can lead to ulceration and lower-limb amputations
- **60%** of lower-limb amputations in adults are caused by type 2 diabetes



Macrovascular

Cardiovascular disease

- Includes angina, CAD, MI, stroke, PAD and CHF
- People with diabetes are **two to three times** more likely to have CVD

Microvascular

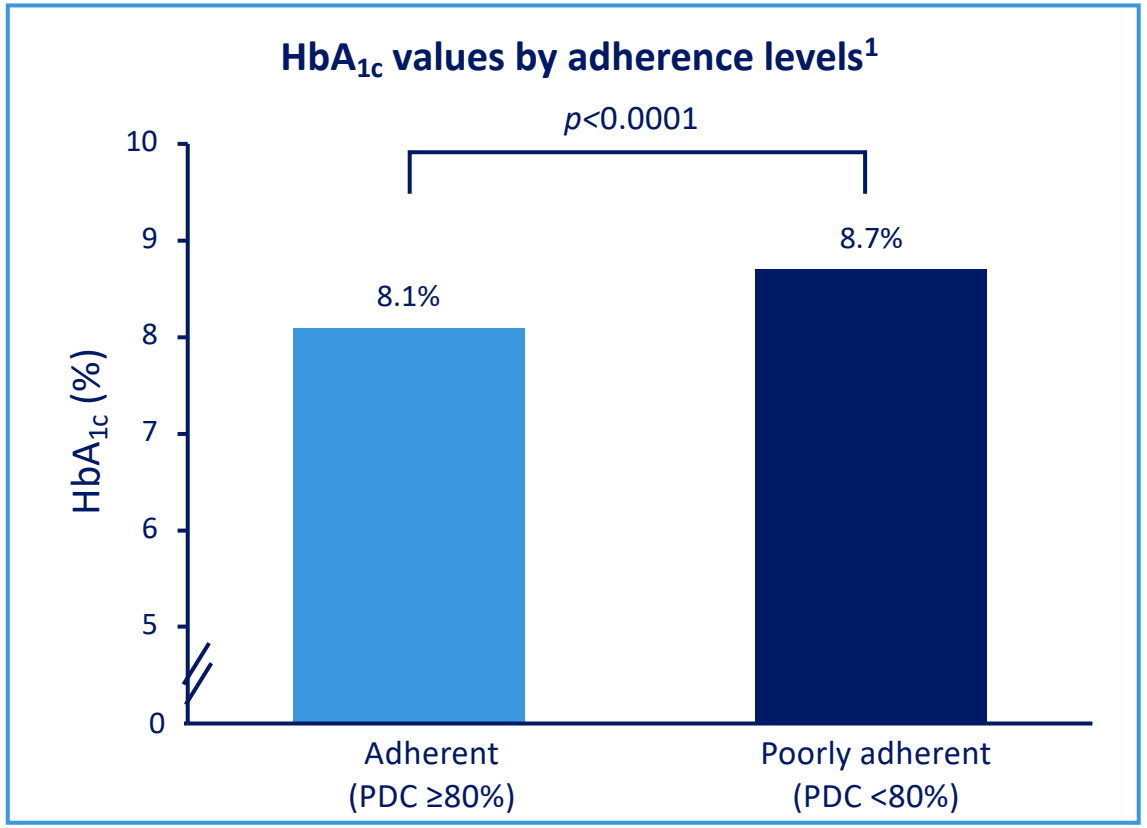
Diabetic nephropathy

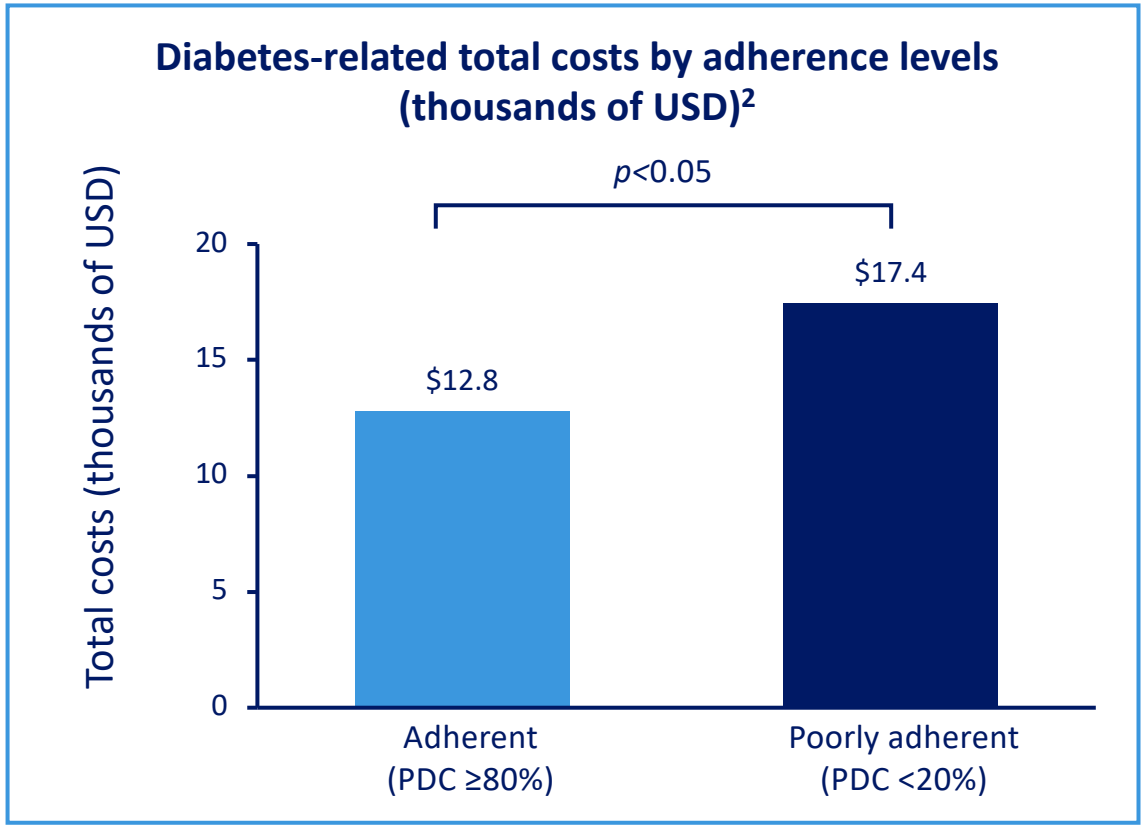
- Diabetes is a **leading** cause of chronic kidney disease and both conditions are interlinked

CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral artery disease.

1. IDF Diabetes Atlas (9th edition). International Diabetes Federation. 2019. http://www.diabetesatlas.org/. Accessed 23 May 2022.

Poor adherence is associated with poor glycaemic control and higher healthcare costs





PDC, proportion of days covered; USD, United States dollar.

1. Donnelly LA et al. *QJM*. 2007;100(6):345–350; 2. Boye KS et al. *Patient Prefer Adherence*. 2016;10:1573–1581.

The recent shift of patient-centric innovation to improve treatment adherence

Poor treatment adherence can lead to:[1]

- Worsening glycaemic control
- Increased hospitalisations, diabetes-related complications and healthcare costs

Some strategies that may improve adherence:[1–6]

- ***Reduced dosing frequency***
- More convenient delivery with improved devices/formulations
- Better tolerability profiles
- Shared decision-making between patient and physician

1. Giorgino F et al. *Patient Prefer Adherence*. 2018;12:707–719; 2. Polonsky WH et al. *Diabetes Obes Metab*. 2011;13(2):144–149; 3. Qin L et al. *Diabetes Ther*. 2017; 8(2):321–334; 4. Best JH et al. *Diabet Med*. 2009;26(7):722–728; 5. Nguyen H et al. *Adv Ther*. 2017; 34(3):658–673; 6. Johnston SC et al. *Adv Ther*. 2014;31(11):1119–1133.

STAY Study
Daily vs Once-Weekly GLP-1 RAs in T2D

Treatment adherence was greater with once-weekly vs daily GLP-1 RAs in T2D

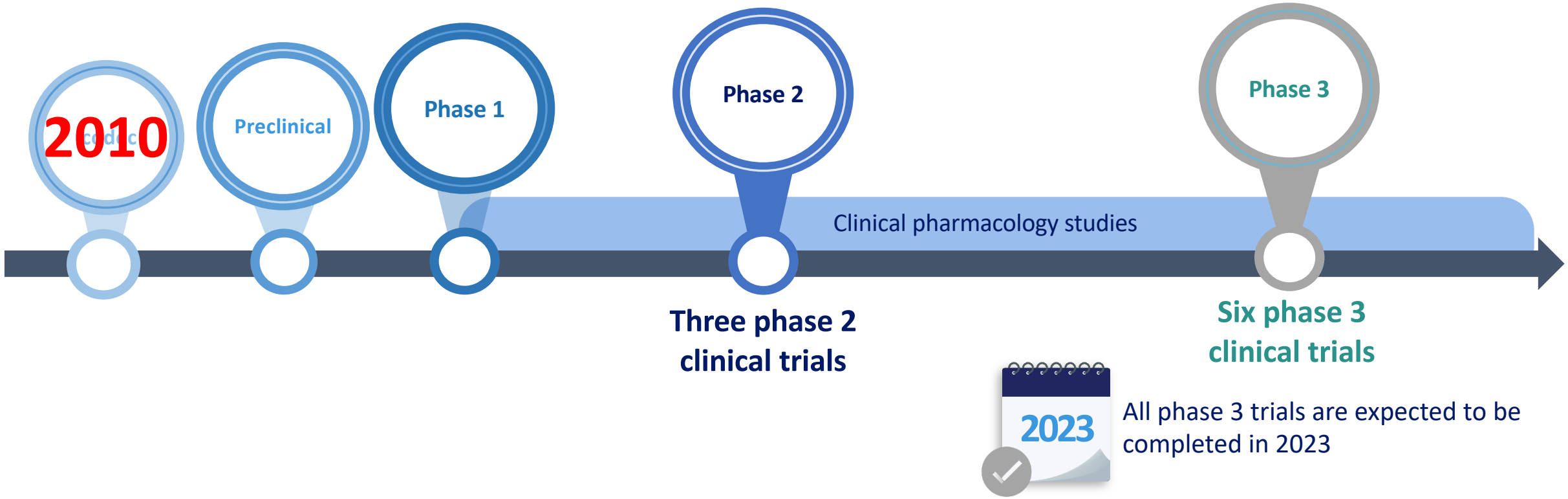
Number of patients adherent (n)	427	343	361	263

Adherence was defined as proportion of days covered of ≥ 0.8.

Polonsky WH, et al. Diabetes Ther. 2022;13:175-187.

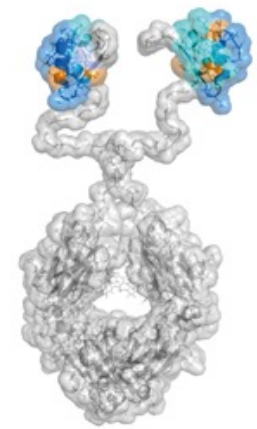
The icodec clinical development programme

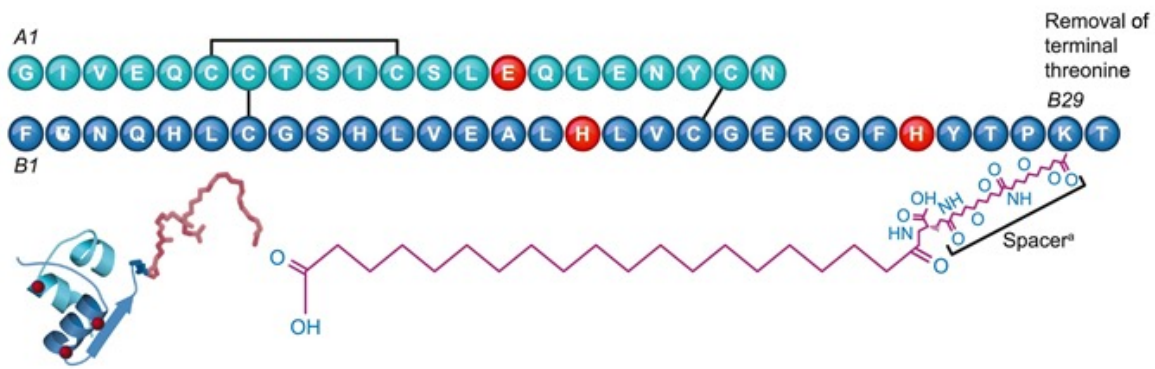
ONWARDS
insulin icodec | a once weekly insulin analogue exploring new options for diabetes treatment



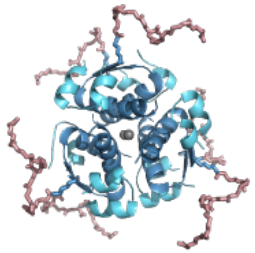
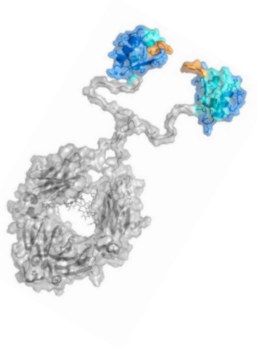
All phase 3 trials are expected to be completed in 2023

A





Overview of once-weekly insulins in development

Insulin icodec		Basal insulin Fc (BIF)
Hexamer of modified human insulin with a **fatty diacid moiety** • Three amino acid substitutions • Albumin-binding C20 icosane fatty diacid side chain • Terminal threonine removed		 Fusion protein of a **single-chain** variant of **insulin** with a **human IgG_2 Fc domain**
Gradual, continuous release of active icodec from albumin-bound inactive depot prolongs activity and buffers against dosing variations	**Mechanism of protraction**	Immunoglobulin Fc domain extends plasma half-life
8 days[1]	**Half-life**	17 days[2]

BIF, basal insulin Fc; Fc, fragment crystallisable region; IgG_2, immunoglobulin G2.

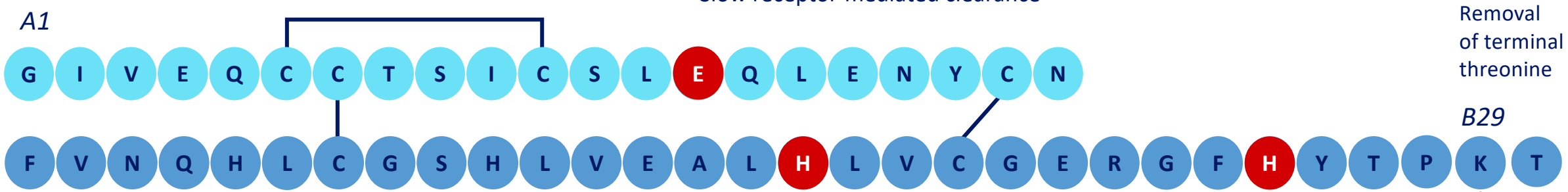
1. Nishimura E et al. *BMJ Open Diabetes Res Care* 2021;9:e002301; 2. Heise T et al. *J Endocr Soc* 2021;5(Suppl 1):A329.
BIF molecule from Rosenstock J and Del Prato S. Metabolism Clinical and Experimental 2022;126:15492

Icodec

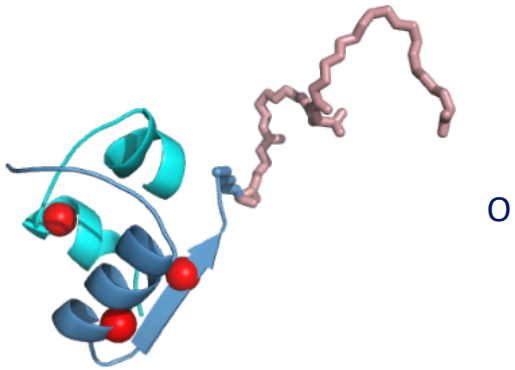
Designed to achieve a long half-life by changes to the human insulin molecule

Three amino acid substitutions

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



Removal of terminal threonine



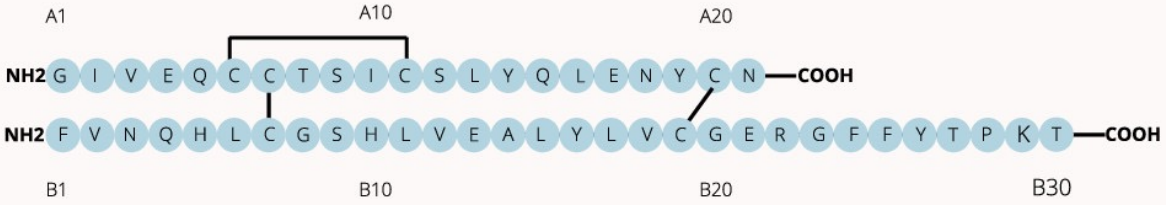
C20 icosane fatty diacid

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

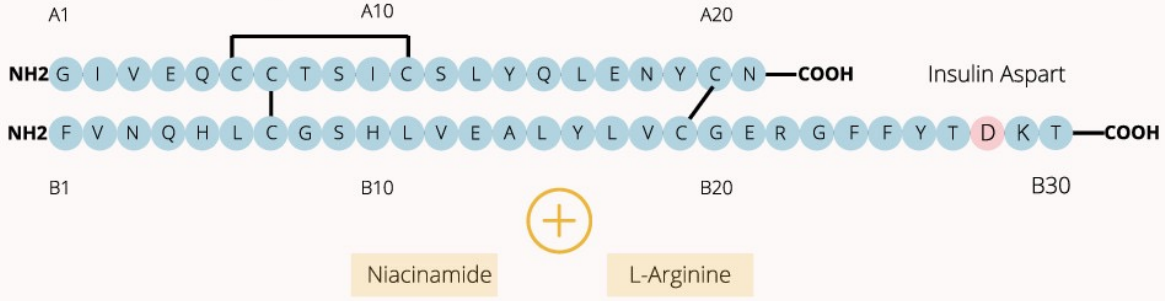
*2x (oligoethylene glycol(OEG) γ-L-Glu) spacer.

1. Kjeldsen TB et al. 2021. *J Med Chem*.64(13):8942-8950.

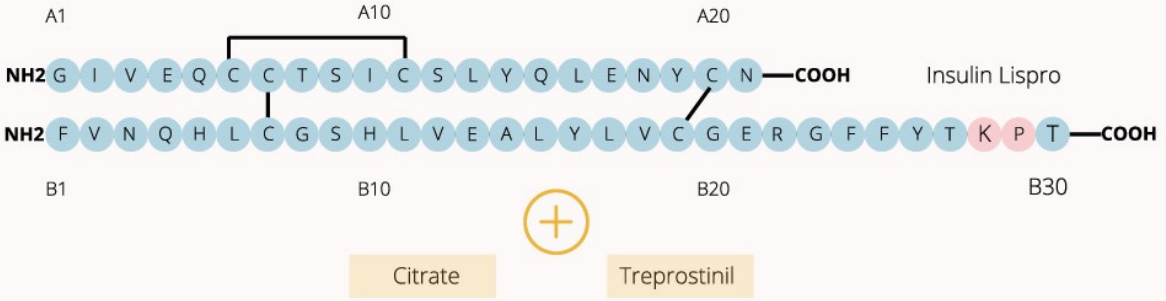
A. Human insulin



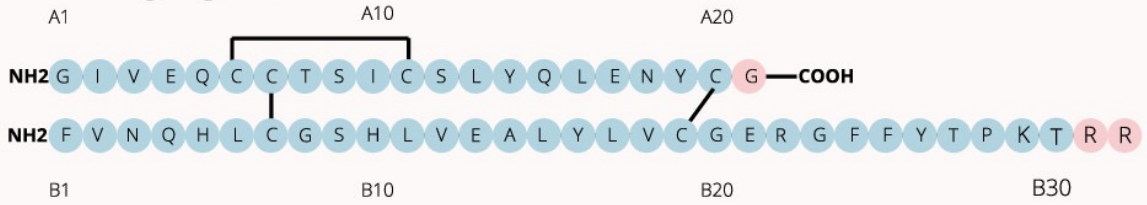
B. Faster insulin aspart



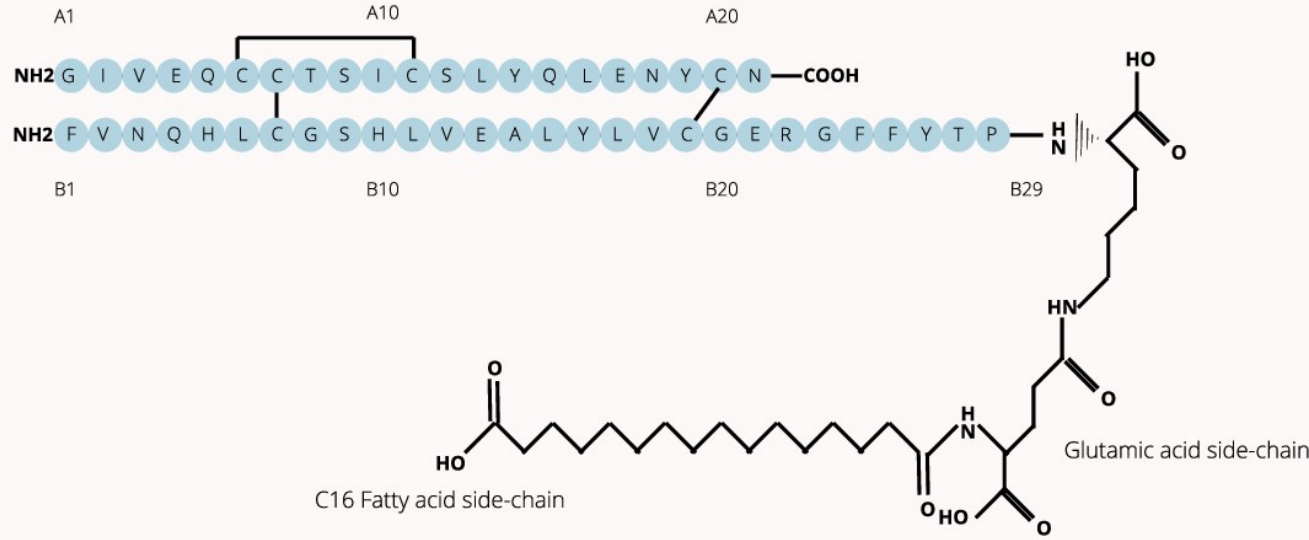
C. Faster insulin lispro-aabc



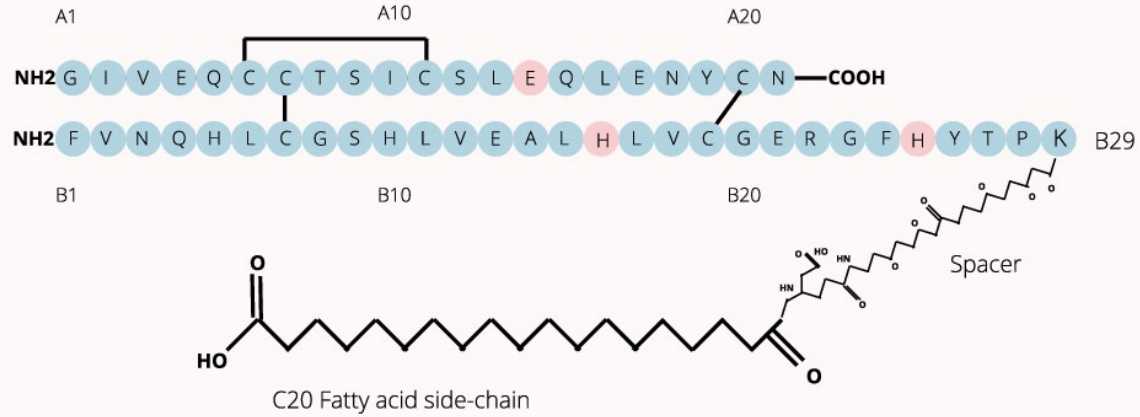
D. Insulin glargine U-100



E. Insulin degludec

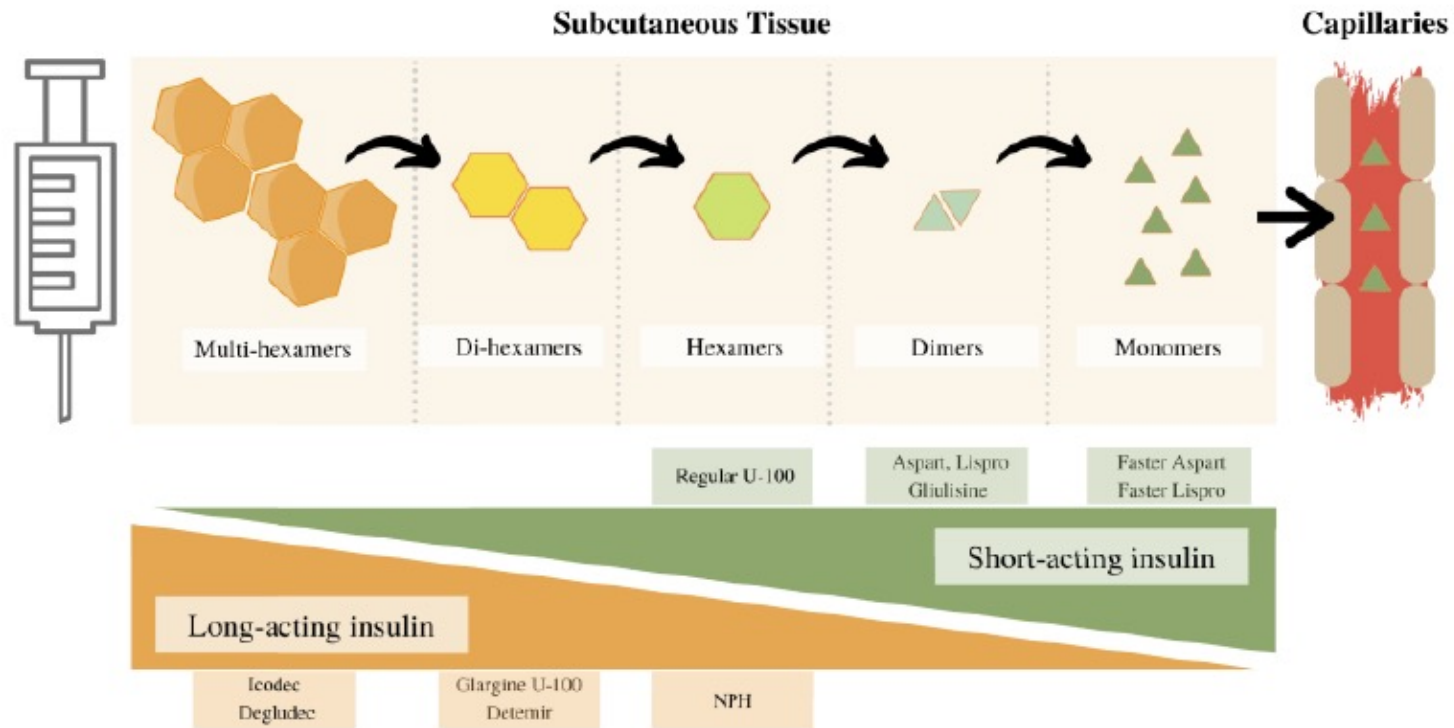


F. Insulin icodec



Legend Amino acid susbstitution

The Promising Future of Insulin Therapy in Diabetes Mellitus



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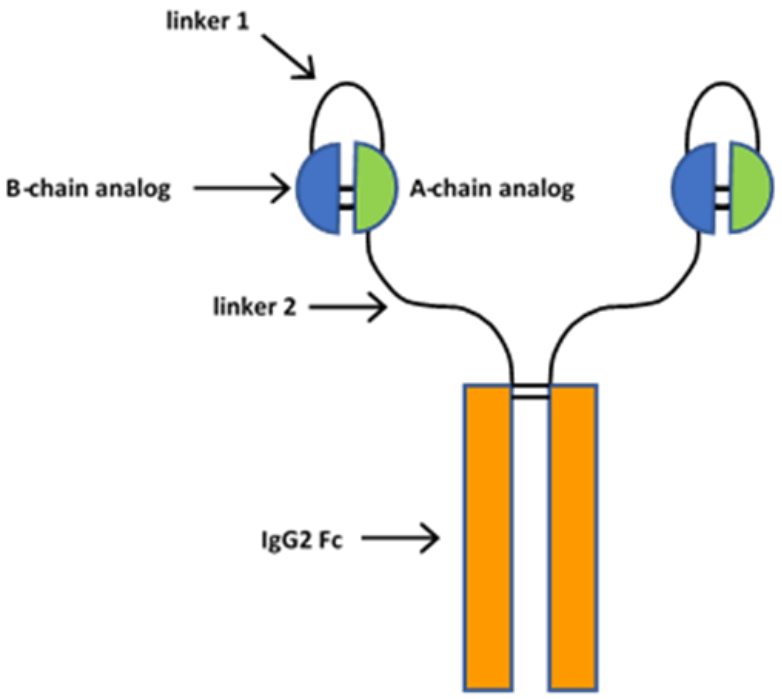
ENDOCRINOLOGY AND METABOLISM.

american physiological society

WEEKLY BASAL INSULIN FC (BIF)

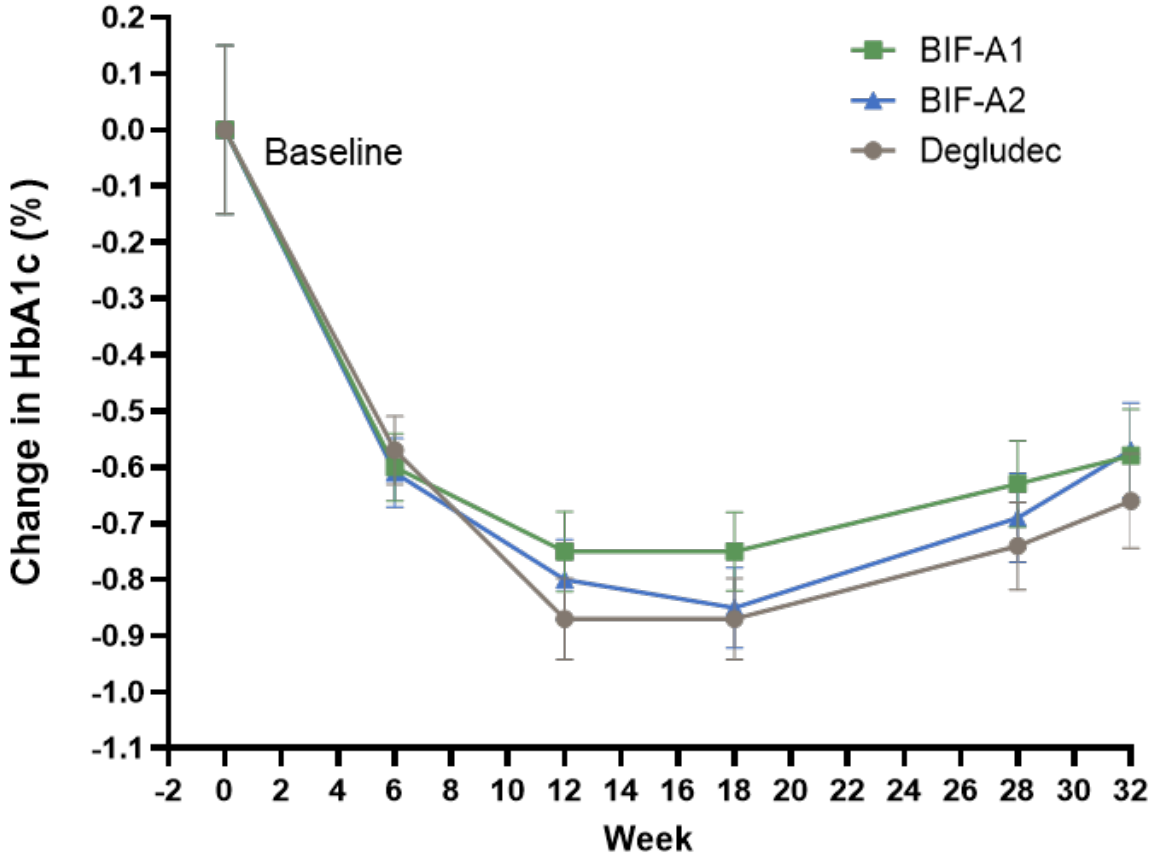
Weekly basal insulin Fc (BIF, insulin efsitora alfa) is an insulin receptor agonist that combines a novel single-chain variant of insulin with a human IgG2 Fc domain. It is designed for once weekly subcutaneous administration.

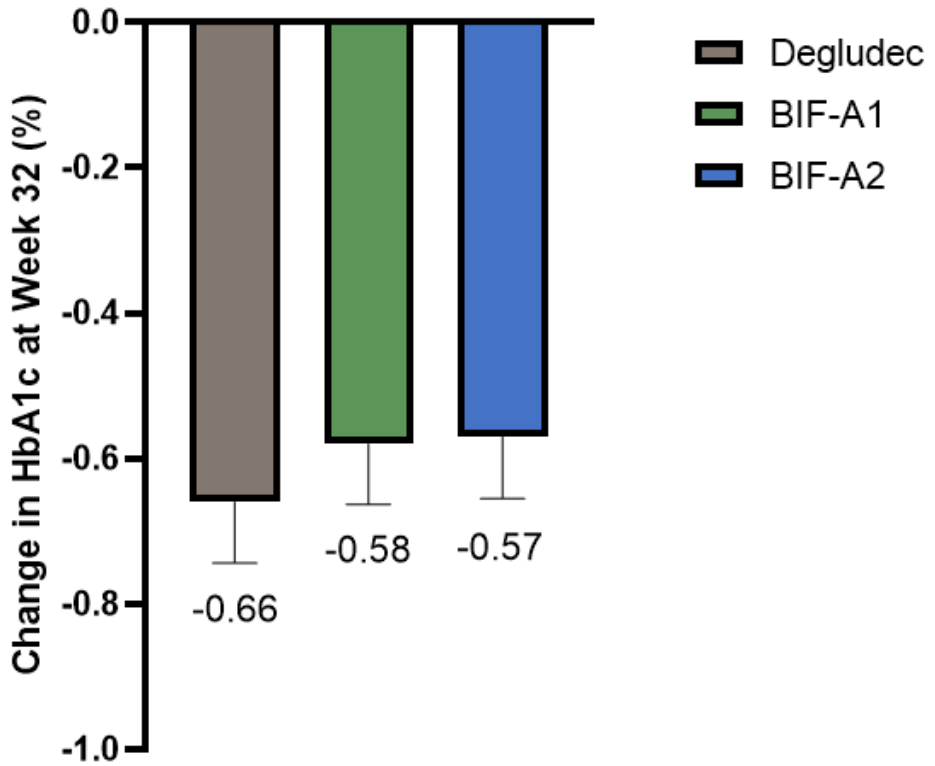


Attributes

- Selective insulin receptor agonist
- Designed for once-weekly SC administration
  - Mean half life: 17 days
  - Weekly peak-to-trough ratio: 1.14
  - Reduced affinity for the insulin receptor resulting in low receptor mediated clearance
  - Large molecule (molecular weight 64.1 kDa) likely with reduced renal clearance
  - FcRn binding prolongs BIF activity

Change From Baseline HbA1c

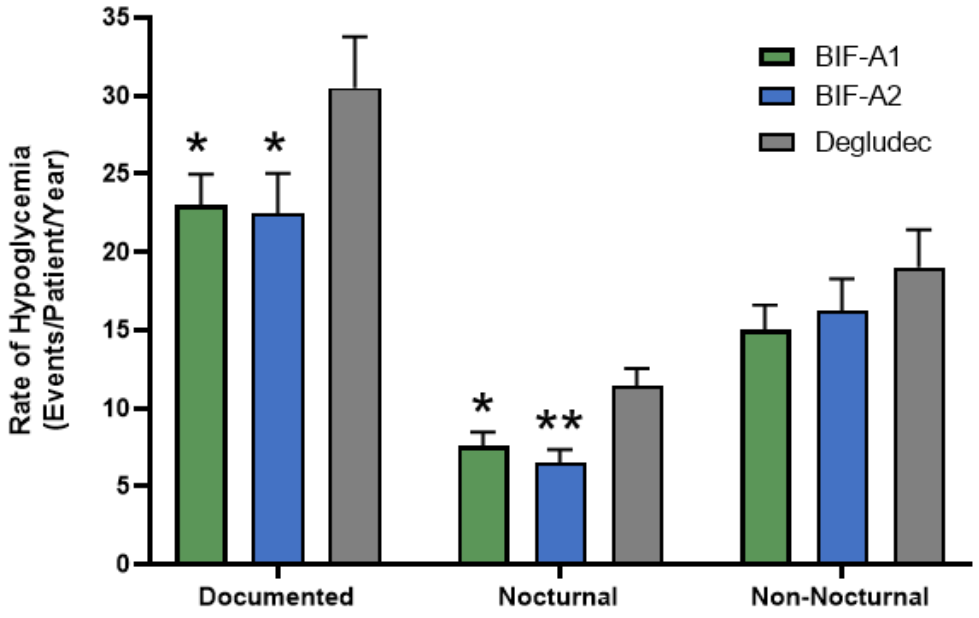


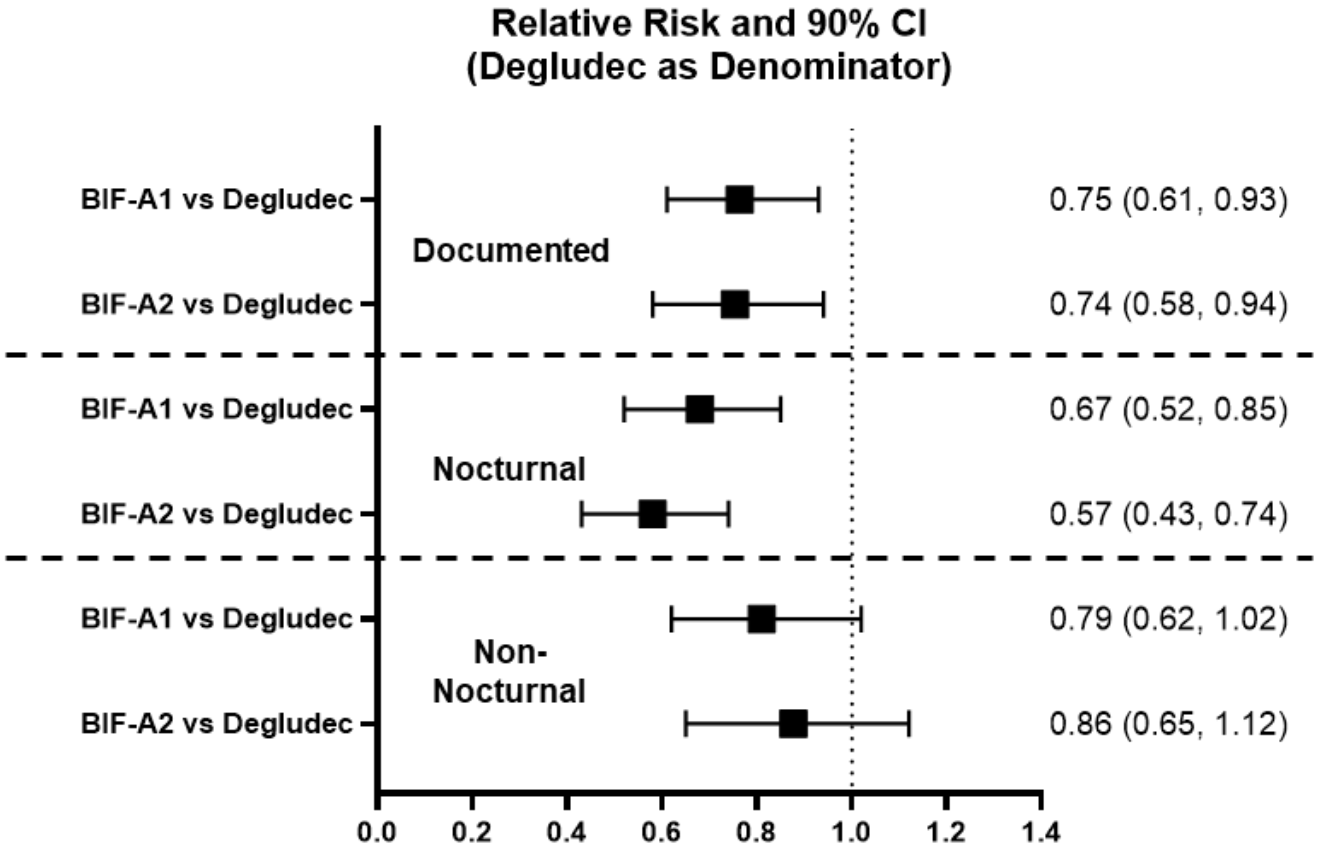


- BIF was noninferior to Degludec for glycemic control as measured by change in HbA1c after 32 weeks
  - Difference: BIF-A1 - Degludec = 0.08[-0.11,0.28]; BIF-A2 - Degludec 0.09[-0.1, 0.29]
- All treatment groups showed significant improvement from baseline at Week 32 ($p<0.001$)

Data presented as mean ± SE.

Rate of Hypoglycemia ≤70 mg/dL





- BIF had a significantly reduced rate of hypoglycemia (≤70 mg/dL) compared to Degludec

Data presented as mean ± SE. *p<0.05; **p<0.001.

Trial design

Icodec in insulin-naïve T2D

247 individuals

- Insulin-naïve T2D on metformin ± DPP-4i
- HbA_{1c} 7.0–9.5% (53–80.3 mmol/mol)
- Age 18–75 years

Weekly icodec + daily placebo + metformin ± DPP-4i

Daily glargine U100 + weekly placebo + metformin ± DPP-4i

Trial information

- Randomised, double-blind, double-dummy, treat-to-target, parallel group
- Blinded FGM (FreeStyle Libre Pro) data during last 2 weeks of treatment
- Starting dose of icodec: 70 U/week
- Starting dose of glargine U100: 10 U/day

Primary trial objective

- To investigate the efficacy of once-weekly icodec on glycaemic control after 26 weeks

Secondary trial objective

- To assess the safety and tolerability of once-weekly icodec during 26 weeks of treatment

Primary endpoint

- Change in HbA_{1c} from baseline to week 26

DPP-4i, dipeptidyl peptidase-4 inhibitor; FGM, flash glucose monitoring; U, unit(s).

1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116.

Titration algorithm

Icodec in insulin-naïve T2D

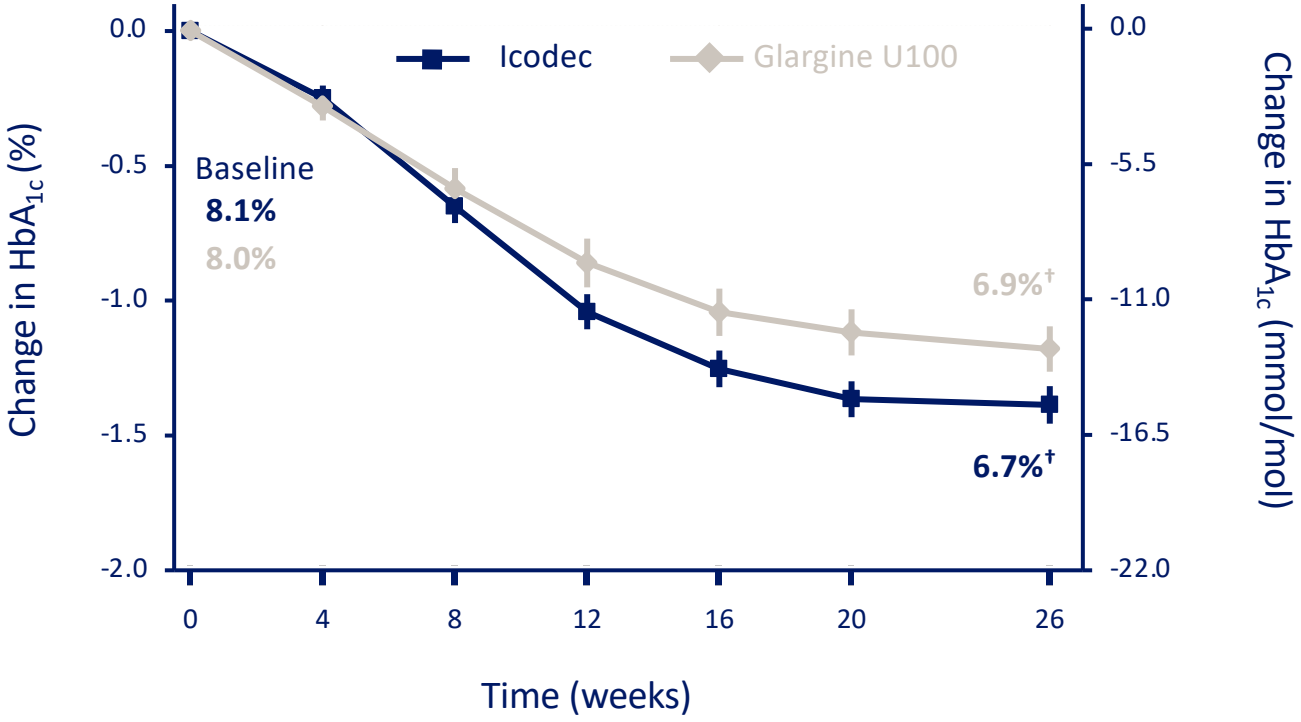
	Pre-breakfast SMBG*	Icodec weekly dose adjustment	Glargine U100 daily dose adjustment
Up-titration	**>7.0 mmol/L** (>126 mg/dL)	**+28 U**	**+4 U**
	6.1–7.0 mmol/L (109–126 mg/dL)	**+14 U**	**+2 U**
Target	**3.9–6.0 mmol/L** (70–108 mg/dL)	**0 U**	**0 U**
Down-titration	**3.0–3.8 mmol/L** (54–69 mg/dL)	**–14 U**	**–2 U**
	<3.0 mmol/L (<54 mg/dL)	**–28 U**	**–4 U**

*Dose adjustment was based on three pre-breakfast SMBG values, measured two days prior to and on the day of titration. If any of the three pre-breakfast SMBG values were below the lower limit of the target range, titration was based on the lowest recorded value. If all three SMBG values were above the lower limit of the target range, titration was based on the mean of the three measurements. SMBG, self-measured blood glucose; U, unit(s).

1. Rosenstock J et al. *N Engl J Med*. 2020; 383:2107–2116.

HbA_{1c} change over time

Icodec in insulin-naïve T2D



	Estimated mean change from baseline to week 26 (%)	ETD vs. glargine U100	
		ETD (%)	95% CI
Icodec	–1.33	–0.18	[–0.38; 0.02]
Glargine U100	–1.15	–	–

No statistically significant difference between treatments in change from baseline to week 26

†Estimated mean HbA_{1c} at week 26. Full analysis set. Observed data are mean (symbol) ± SEM (error bars) on-treatment without ancillary treatment. ETD: icodec – glargine U100. Estimated means, mean change values and ETD with 95% CI at week 26 derived based on MMRM (trial product estimand).

CI, confidence interval; ETD, estimated treatment difference; MMRM, mixed model for repeated measures; SEM, standard error of the mean.

1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116.

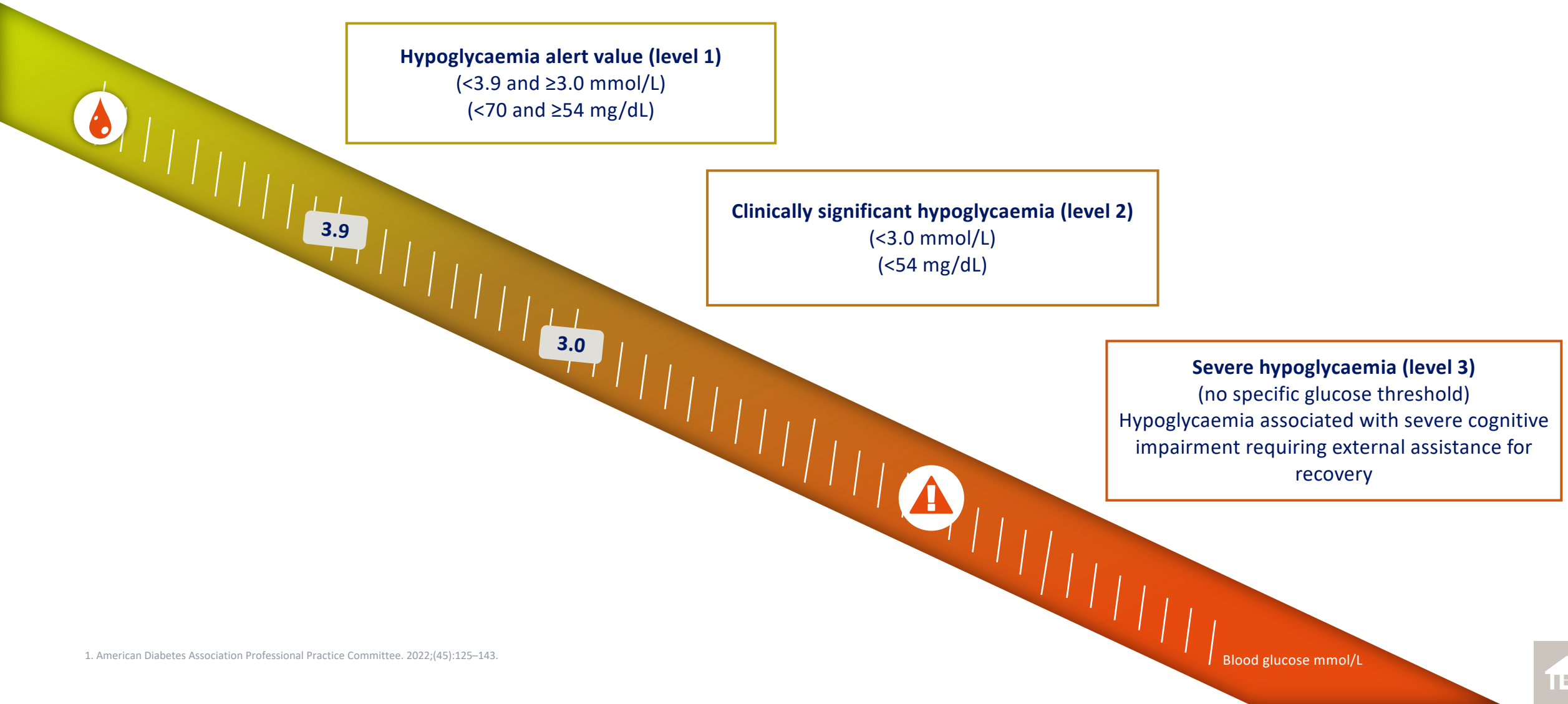
Hypoglycaemia classification

Icodec phase 2 trials

Hypoglycaemia alert value (level 1)
(<3.9 and ≥3.0 mmol/L)
(<70 and ≥54 mg/dL)

Clinically significant hypoglycaemia (level 2)
(<3.0 mmol/L)
(<54 mg/dL)

Severe hypoglycaemia (level 3)
(no specific glucose threshold)
Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

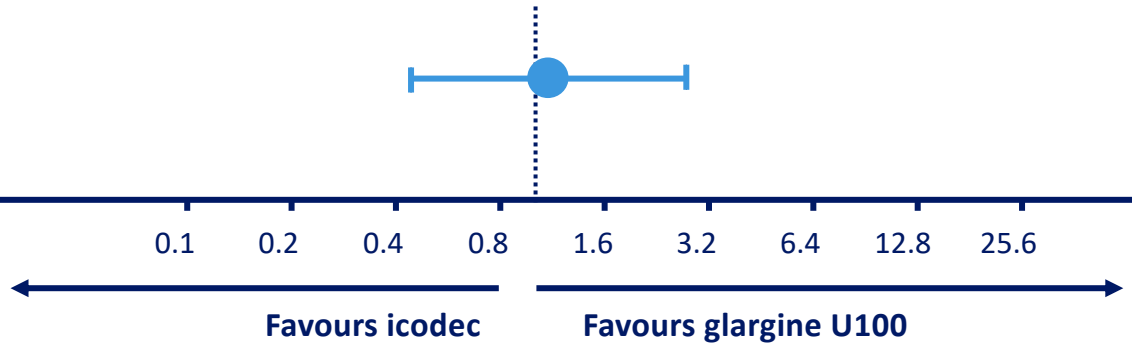


1. American Diabetes Association Professional Practice Committee. 2022;(45):125–143.

Hypoglycaemia (level 2 + 3) during the on-treatment period

Icodec in insulin-naïve T2D

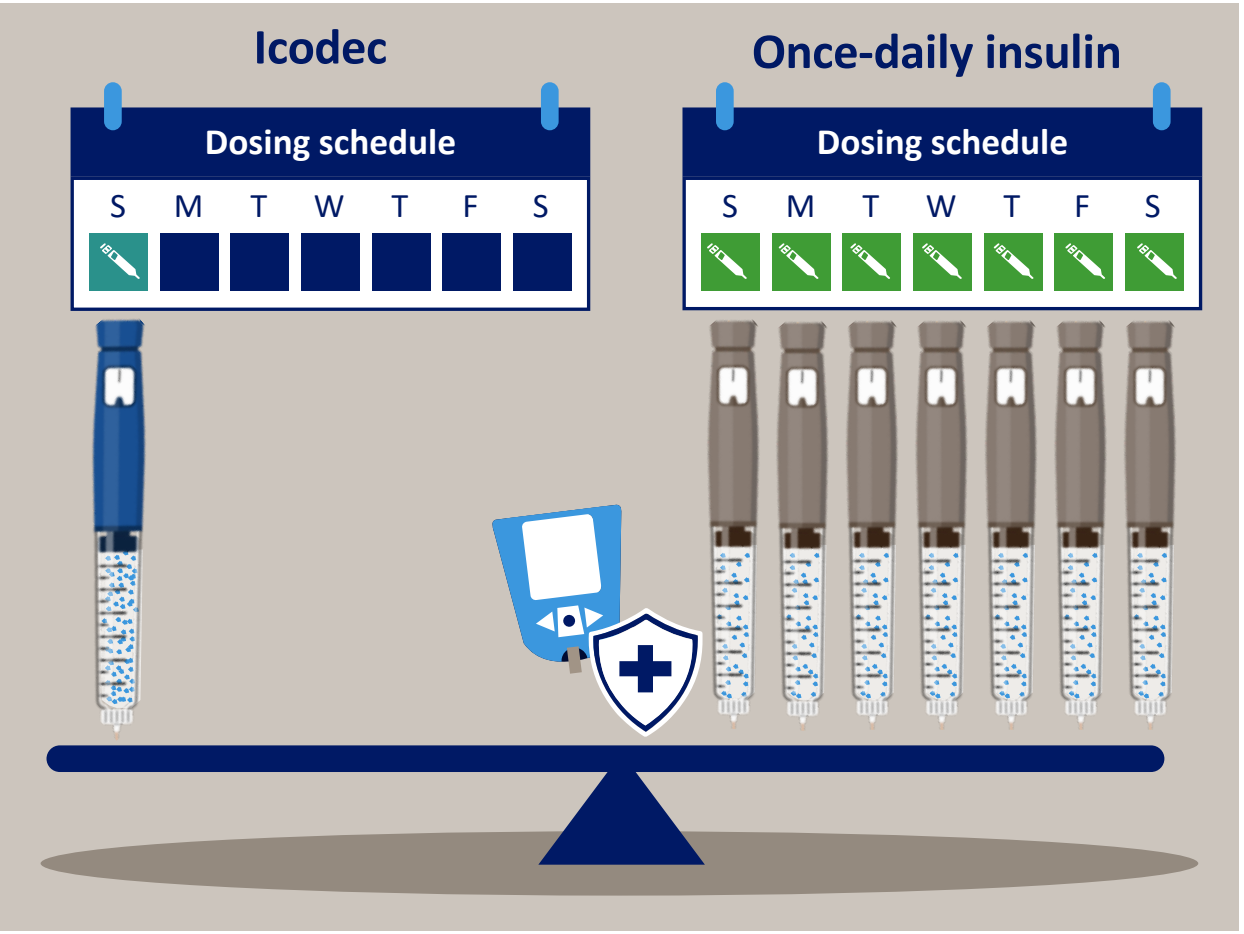
Severe (level 3) or clinically significant (level 2) hypoglycaemia	ERR† icodec/glargine U100	95% CI
On-treatment period	1.09	[0.45; 2.65]



No statistically significant difference between icodec and glargine U100

†Prespecified analysis for combined level 3 or level 2 hypoglycaemia.
Full analysis set. On-treatment: onset date on or after the first dose of trial product and no later than the first date of either the last follow-up visit (FU2), the last date on trial product + 5 weeks for once-daily insulin and + 6 weeks for once-weekly insulin or the end-date for the in-trial period.
Number of events was analysed using a negative binomial regression model (log link).
CI, confidence interval; ERR, estimated rate ratio.
1. Rosenstock J et al. *N Engl J Med*. 2020;383:2107–2116.

Clinical application of icodec



- One injection per week compared to seven injections with once-daily insulin
- The formulation (700 U/mL) ensures the **injection volume** is **similar** to once-daily basal insulin
- **Weekly coverage** is achieved by the gradual release of icodec from albumin-bound depot
- Recent data demonstrate that glycaemic control, safety, and dose requirements are **comparable to once-daily insulin**

U, unit(s).

Trial design

Icodec titration trial in insulin-naïve T2D

205 individuals

- Insulin-naïve T2D on metformin ± DPP-4i ± SGLT-2i
- HbA_{1c}: 7.0–10.0% (53–86 mmol/mol)
- Aged 18–75 years
- Stratified by SGLT-2i use

Icodec titration A	target 4.4–7.2 mmol/L (80–130 mg/dL), adjust ± 21 U/week
Icodec titration B	target 4.4–7.2 mmol/L (80–130 mg/dL), adjust ± 28 U/week
Icodec titration C	target 3.9–6.0 mmol/L (70–108 mg/dL), adjust ± 28 U/week
Glargine U100	target 4.4–7.2 mmol/L (80–130 mg/dL), adjust ± 4 U/day

Trial information

- Randomised, open-label, treat-to-target design
- Double-blinded CGM (Dexcom G6®)
- Starting dose of icodec: 70 U/week
- Starting dose of glargine U100: 10 U/day

Trial objective

- To evaluate the efficacy and safety of three different titration algorithms for once-weekly icodec versus once-daily insulin glargine U100 after 16 weeks of treatment

Primary endpoint

- Time-in-range 3.9–10.0 mmol/L (70–180 mg/dL) during the last 2 weeks of treatment

Secondary endpoints

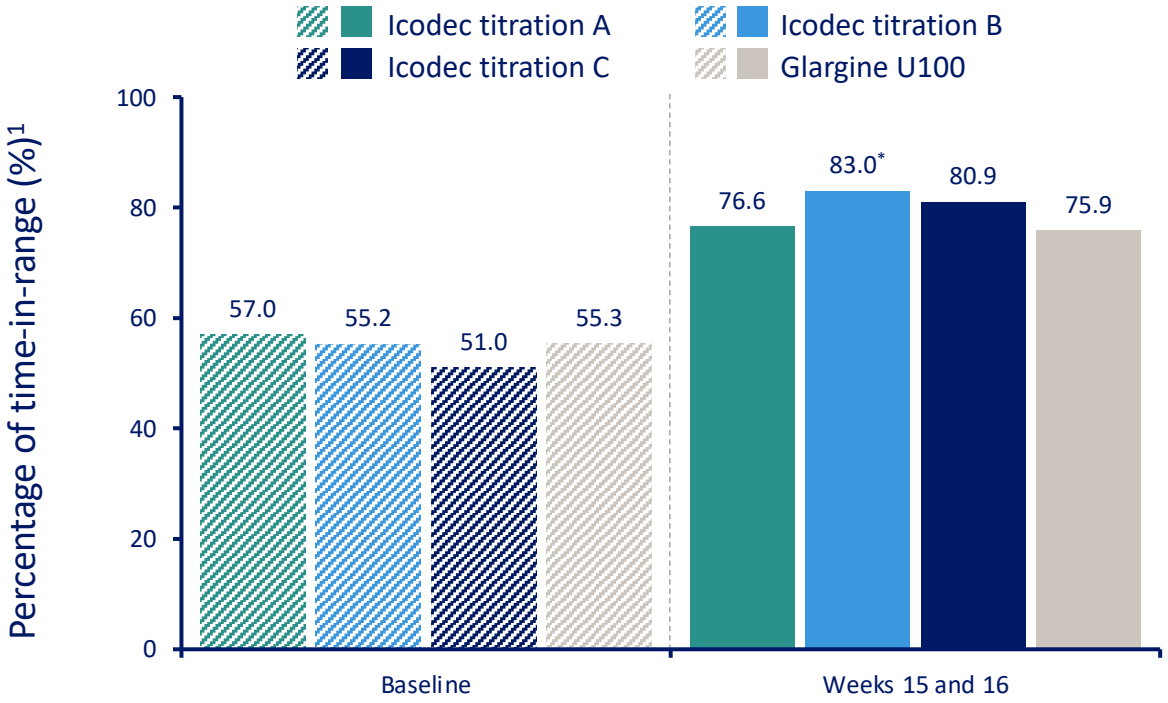
- Change from baseline to week 16 in HbA_{1c}
- Change from baseline to week 16 in FPG
- Weekly insulin dose during the last 2 weeks of treatment
- Change from baseline to week 16 in body weight
- Hypoglycaemic episodes

CGM, continuous glucose monitoring; DPP-4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; U, unit(s).

1. Lingvay I et al. *Diabetes Care*. 2021;44(7):1595–1603.

Primary endpoint: TIR during weeks 15 and 16

Icodec titration trial in insulin-naïve T2D



$TIR_{3.9–10.0\ mmol/L\ (70–180\ mg/dL)}$, weeks 15 & 16[2]

ETD vs. glargine U100

	ETD (%)	95% CI
Icodec titration A	0.76	[–4.28; 5.80]
Icodec titration B	7.08	[2.12; 12.04]*
Icodec titration C	5.01	[–0.04; 10.05]

TIR was statistically significantly longer for icodec titration B compared to glargine U100

*p=0.005. FAS, n=205. Baseline values are observed mean values. Weeks 15 & 16 (end of treatment) values represent estimated mean values. Estimated mean values are derived based on an analysis of covariance model with multiple imputation from own treatment arm (trial product estimand).

CI, confidence interval; ETD, estimated treatment difference; FAS, full analysis set; n, number of subjects; TIR, time-in-range.

1. Lingvay I et al. *Diabetes Care*. 2021;44(7):1595–1603.

Hypoglycaemic episodes

Icodec titration trial in insulin-naïve T2D

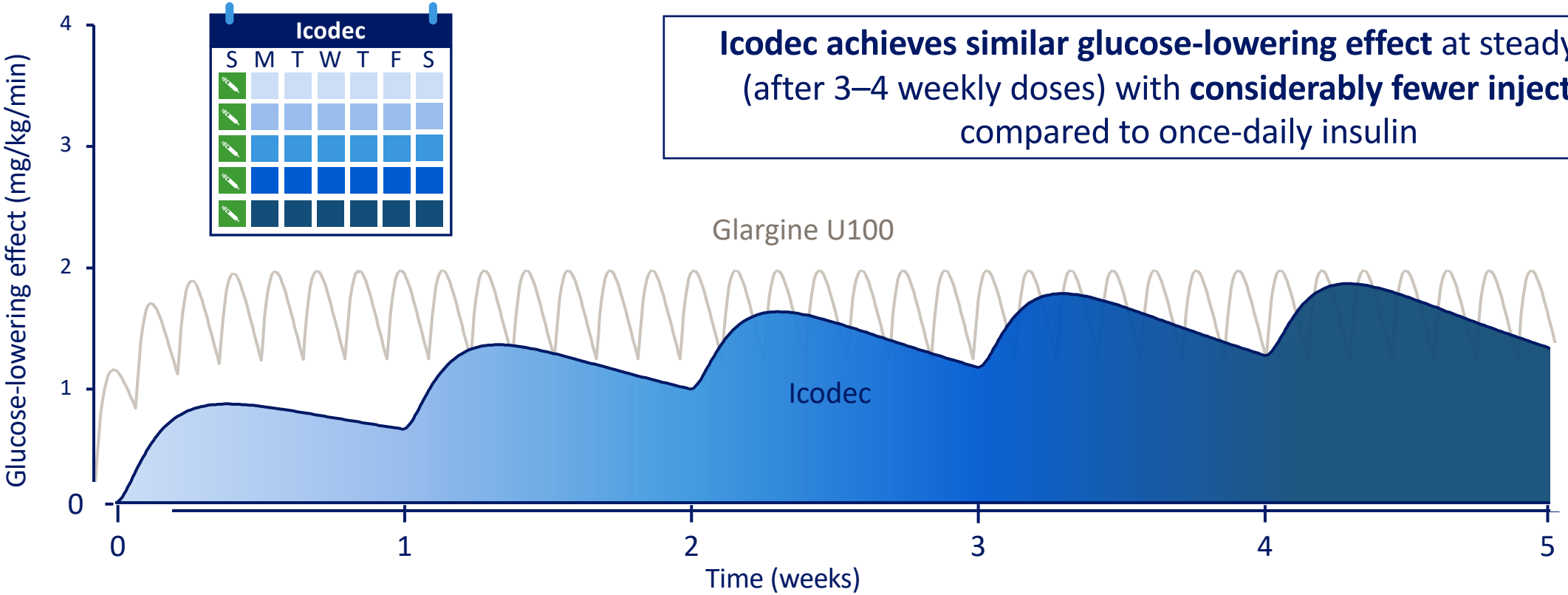
	Icodec **Titration A** (n=51)				Icodec **Titration B** (n=51)				Icodec **Titration C** (n=52)				Glargine U100 (n=51)			
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
Level 1	7	(13.7)	15	0.73	10	(19.6)	23	1.11	29	(55.8)	113	5.38	9	(17.6)	12	0.58
Level 2 + Level 3	1	(2.0)	1	0.05	3	(5.9)	3	0.15	4	(7.7)	8	0.38	0	–	–	–
Level 3	0	–	–	–	0	–	–	–	0	–	–	–	0	–	–	–

The number of combined clinically significant (level 2) or severe (level 3) hypoglycaemic episodes was low for all icodec treatment groups. Level 1 hypoglycaemia was reduced when using the ADA-recommended pre-breakfast target of 4.4–7.2 mmol/L (80–130 mg/dL)

Safety analysis set. Hypoglycaemia alert value (level 1): plasma glucose value of <3.9 mmol/L (<70 mg/dL) and ≥3.0 mmol/L (≥54 mg/dL) confirmed by BG meter. Clinically significant hypoglycaemia (level 2): plasma glucose value of <3.0 mmol/L (<54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
%, percentage of patients with one or more events; ADA, American Diabetes Association; BG, blood glucose; E, number of events; N, number of patients with one or more events; n, number of subjects; R, rate (number of events per patient-year of exposure).
1. Lingvay I et al. *Diabetes Care*. 2021;44(7):1595–1603.

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

Based on phase 1 clinical data



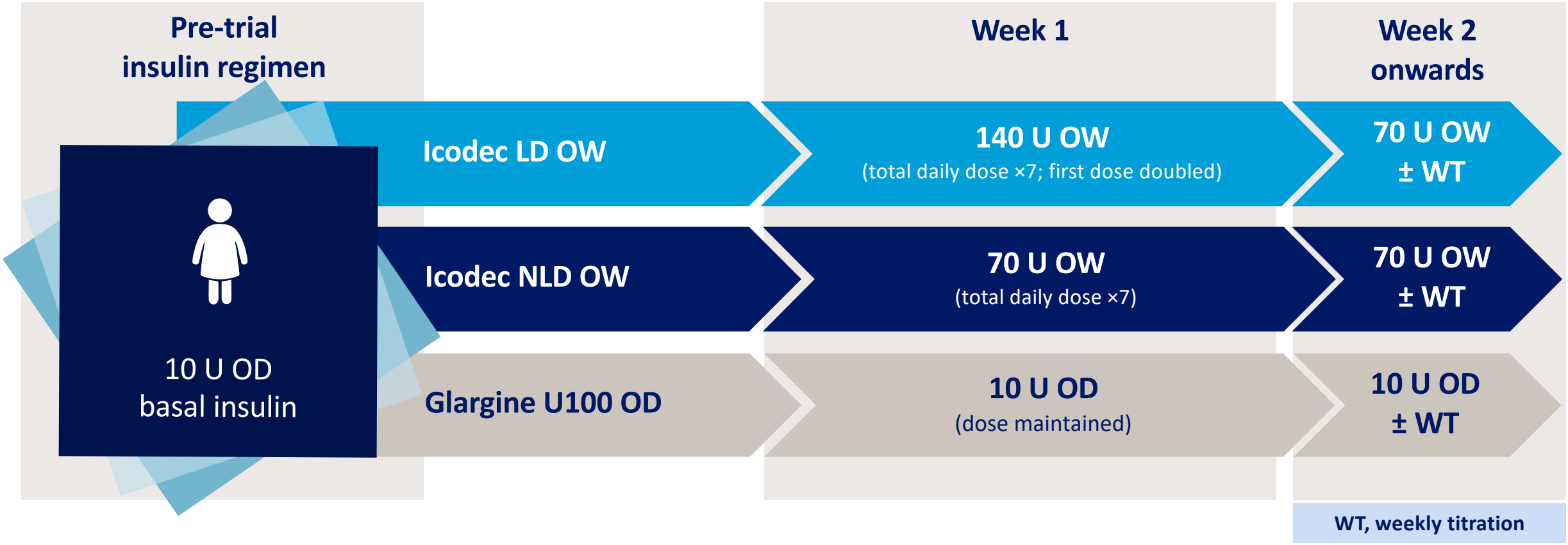
Icodec achieves similar glucose-lowering effect at steady state (after 3–4 weekly doses) with **considerably fewer injections** compared to once-daily insulin

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.

Hypothetical case: switching from OD basal insulin

Switching from OD/BID basal insulin to OW icodec



BID, twice-daily; LD, loading dose; NLD, no loading dose; OD, once-daily; OW, once-weekly; U, unit(s); WT, weekly titration.

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

Trial design

Switching from OD/BID basal insulin to OW icodec

154 individuals

- T2D treated with basal insulin (10–50 U/day) + metformin ± DPP-4i ± SGLT-2i
- HbA_{1c}: 7.0–10.0% (53–86 mmol/mol)
- Aged 18–75 years
- Stratified by SGLT-2i use and insulin type*

Once-weekly icodec with 100% loading dose (icodec LD)

Once-weekly icodec with no loading dose (icodec NLD)

Once-daily glargine U100 (glargine U100)

Trial information

- Randomised, open-label, treat-to-target design
- Double-blinded CGM (Dexcom G6®)

Trial objective

- To investigate the safety and the efficacy of two different icodec switch approaches versus glargine U100 after 16 weeks of treatment

Primary endpoint

- Time-in-range 3.9–10.0 mmol/L (70–180 mg/dL) during the last 2 weeks of treatment

Secondary endpoints

- Change from baseline to week 16 in HbA_{1c}
- Change from baseline to week 16 in FPG
- Weekly insulin dose during the last 2 weeks of treatment
- Change from baseline to week 16 in body weight
- Hypoglycaemic episodes

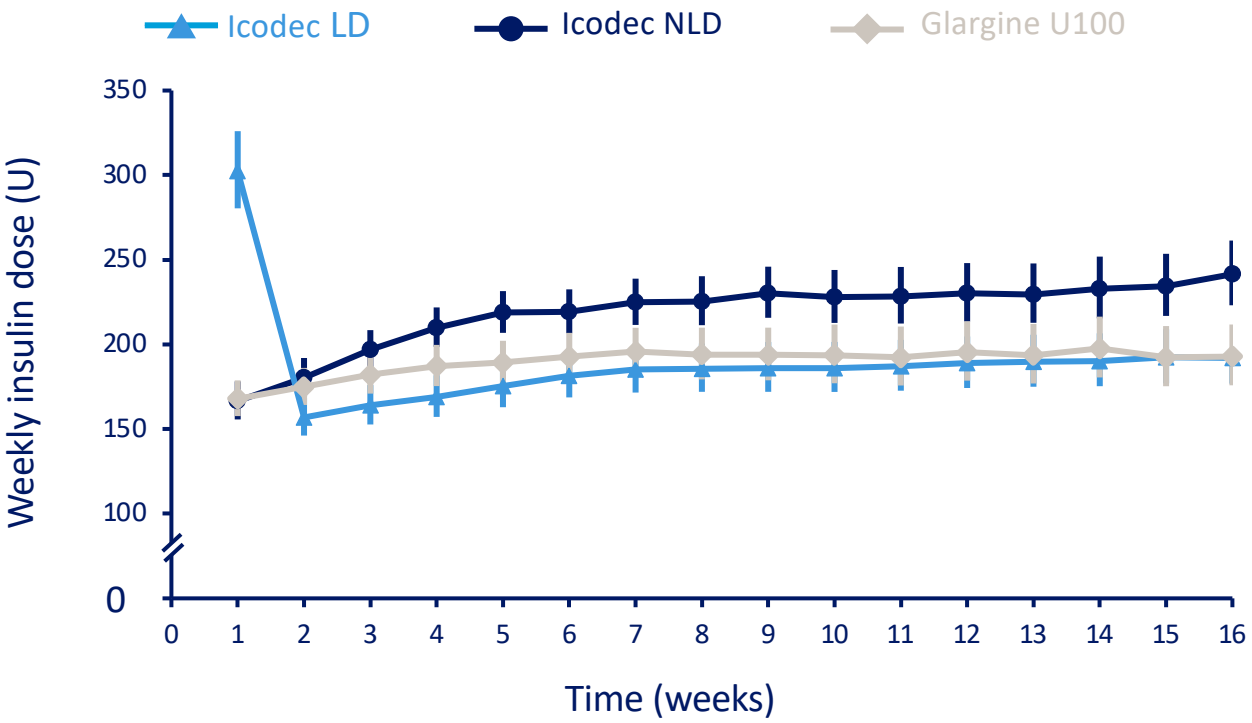
*OD or BID basal insulin/insulin glargine U300.

BID, twice-daily; CGM, continuous glucose monitoring; DPP-4i, dipeptidyl peptidase-4 inhibitor; LD, loading dose; NLD, no loading dose; OD, once-daily; OW, once-weekly; SGLT2i, sodium-glucose cotransporter-2 inhibitor; U, unit(s).

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

Weekly insulin dose over time

Switching from OD/BID basal insulin to OW icodec



Weekly insulin dose during the last 2 weeks of treatment

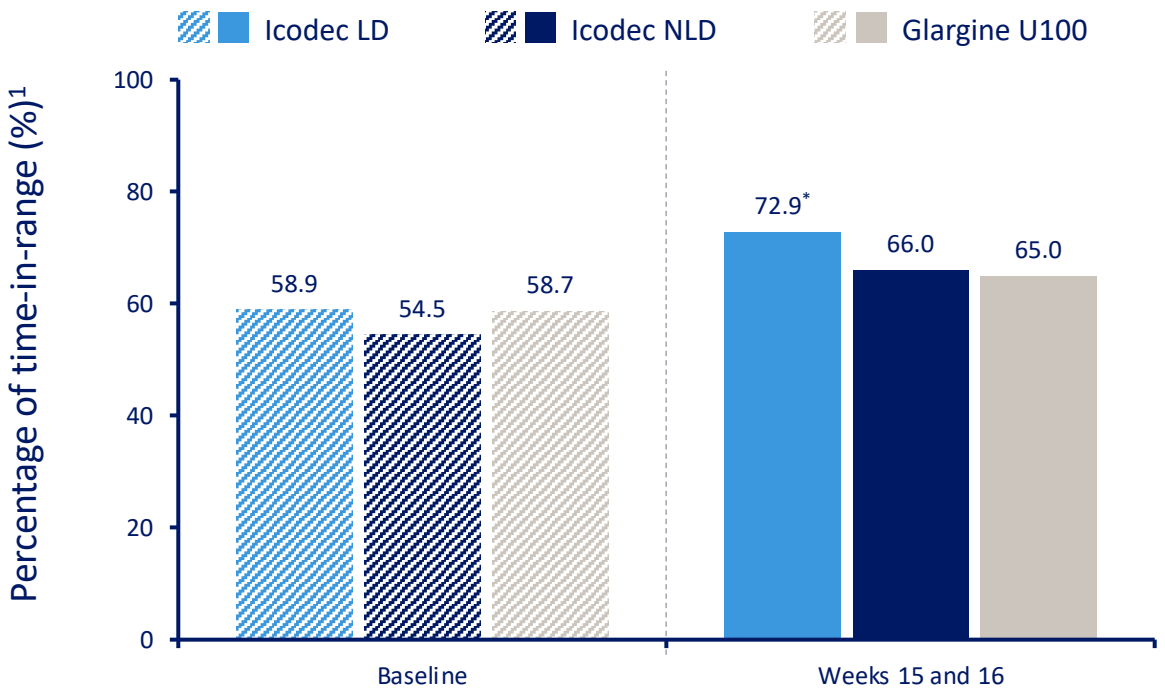
	Estimated mean weekly insulin dose during weeks 15 & 16 (U/week)	ETR vs. glargine U100	
		ETR	95% CI
Icodec LD	191	0.98	[0.78; 1.23]
Icodec NLD	242	1.24	[0.98; 1.56]
Glargine U100	196	–	

There were no statistically significant differences in mean weekly insulin dose seen in icodec groups vs. glargine U100

Full analysis set. Estimated mean weekly insulin doses during weeks 15 and 16 are shown. Weekly glargine U100 dose is derived as 7 times average daily dose during the preceding week.
BID, twice-daily; CI, confidence interval; ETR, estimated treatment ratio; LD, loading dose; NLD, no loading dose; OD, once-daily; OW, once-weekly; U, unit(s).
1. Bajaj H et al. *Diabetes Care*. 2021; 44(7):1586–1594.

Primary endpoint: TIR during weeks 15 and 16

Switching from OD/BID basal insulin to OW icodec



$TIR_{3.9–10.0\ mmol/L\ (70–180\ mg/dL)}$, weeks 15 & 16[2]

ETD vs. glargine U100

	ETD (%)	95% CI
Icodec LD	7.88	[1.83; 13.93]*
Icodec NLD	1.01	[–5.33; 7.5]

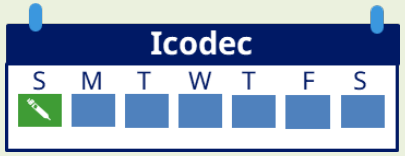
TIR was statistically significantly longer for icodec LD compared to glargine U100

*p=0.01. Full analysis set. Baseline values are observed mean values. Weeks 15 and 16 (end of treatment) values represent estimated mean values. Estimated mean values are derived based on an analysis of covariance model with multiple imputation from own treatment arm (trial product estimand).
BID, twice-daily; CI, confidence interval; ETD, estimated treatment difference; LD, loading dose; NLD, no loading dose; OD, once-daily; OW, once-weekly;
TIR, time-in-range.

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

Initiation or switching to icodec in Phase 3 trials

Initiation with icodec



Start at 70 U for weekly coverage

= Starting dose of 10 U OD basal insulin* = 70 U OW icodec

Switching from once-daily insulin to icodec

x7 Multiply daily dose by 7 for weekly dose

For the first injection only, add an initial, one-time additional **50%** icodec dose

In T1D with HbA_{1c} ≥8%, the additional dose should be **100%**

Example: Switching from OD insulin to icodec (T2D)

Daily dose 20 U → **Weekly dose 140 U** (20 U x 7) + **An initial one-time additional 50% icodec dose**

According to ADA guideline. ADA, American Diabetes Association; OD, once-daily; OW, once-weekly; T1D, type 1 diabetes; U, unit(s).

*ADA, Standards of Medical Care 2022.

Highlights from the BIF Phase 2 clinical program

T2D: Initiation trial[1]

Insulin-naïve T2D (n=278)
BIF vs insulin degludec
26 weeks

T2D: Switch and titration trial[2,3]

Basal insulin-treated T2D (n=399)
BIF vs insulin degludec
32 weeks

T1D: Switch trial[4]

Basal-bolus insulin-treated T1D (n=266)
BIF vs insulin degludec
26 weeks

Phase 3 program (QWINT) started in 2022[5]

T2D

Insulin-naïve

QWINT-1
BIF vs insulin glargine (U100)

QWINT-2
BIF vs insulin degludec

Insulin-experienced

QWINT-3
Basal switch
BIF vs insulin degludec

QWINT-4
MDI
BIF vs insulin glargine (U100)

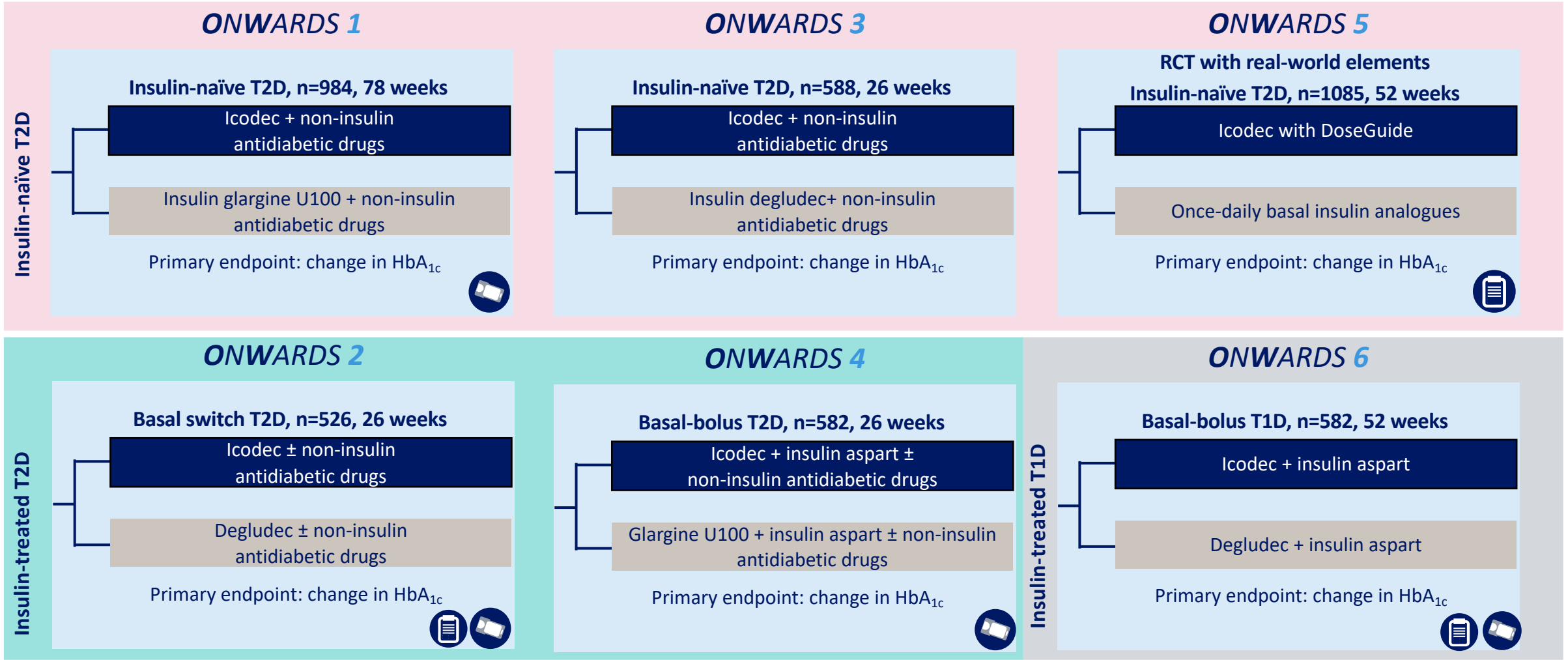
T1D

QWINT-5
MDI
BIF vs insulin degludec

BIF, basal insulin Fc; Fc, fragment crystallisable region; MDI, multiple daily injections; T1D, type 1 diabetes, T2D, type 2 diabetes.

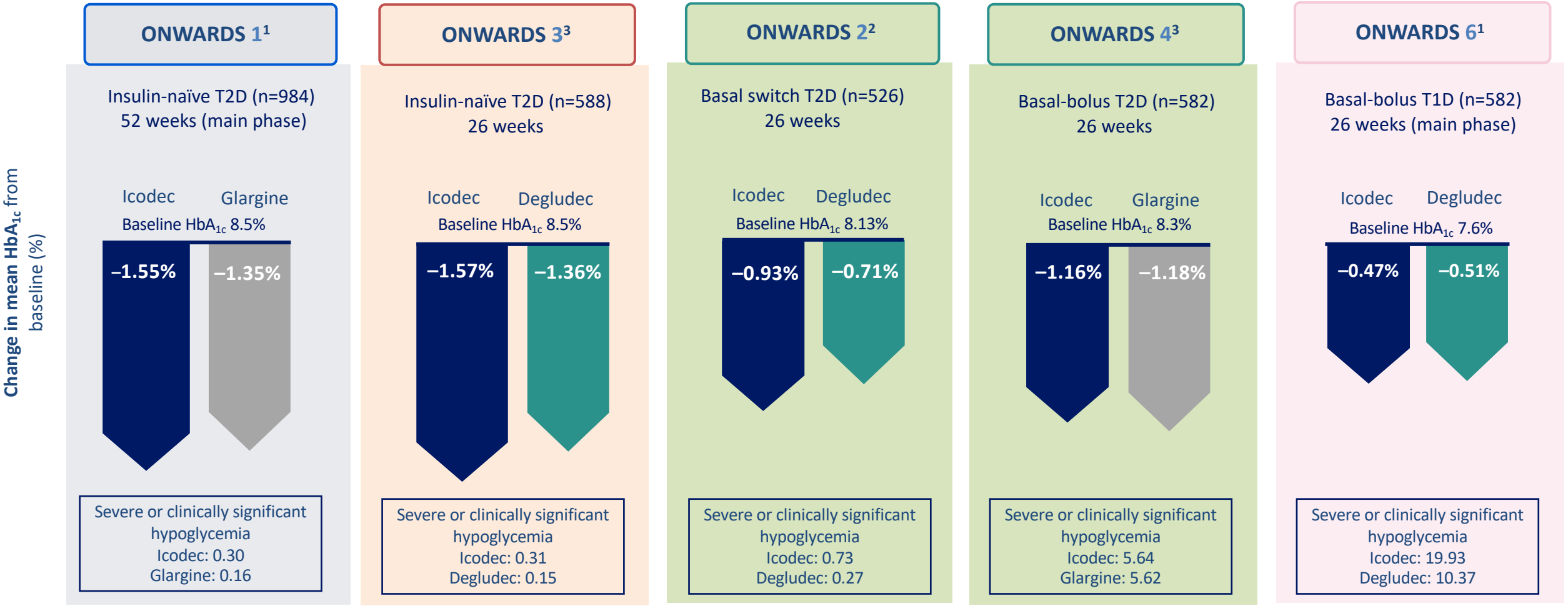
1. Bue-Valleskey J et al. American Diabetes Association 82nd Annual Scientific Sessions; 2. Frias J. Oral presentation at ENDO 2021 OR-09; 3. Clinicaltrials.gov. https://www.clinicaltrials.gov/ct2/show/results/NCT03736785; 4. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04450407;
5. Eli Lilly. Investor Meeting. Available at: https://investor.lilly.com/static-files/34f9ec12-02a9-4452-843e-0501309bde98. All accessed Sep 2022.

Summary of the *ONWARDS* programme



CGM, continuous glucose monitoring; n, number of subjects; PROs, patient reported outcomes; RCT, randomised controlled trial.

ONWARDS 1, 2, 3, 4 and 6 topline results



Glargine in ONWARDS 1 and 4 was the U100 formulation.
ETD, estimated treatment difference; T1D, type 1 diabetes, T2D, type 2 diabetes.

1. Novo Nordisk A/S company announcement, June 3, 2022; 2. Novo Nordisk A/S company announcement, April 28, 2022;
3. Novo Nordisk A/S company announcement, July 29, 2022.

Conclusions

Comparable glycemic control and safety profile with OW insulins as OD insulins in T2D[1]

A titration target of 4.4–7.2 mmol/L (80–130 mg/dL) with insulin icodec secures good glycemic control with low risk of hypoglycemia in T2D[2]

An **initial, one-time additional icodec dose** is relevant when switching from OD basal insulin in T2D[3]

Icodec and BIF are further studied in comprehensive **Phase 3 programs**

BIF, basal insulin Fc; Fc, fragment crystallisable region; OD, once-daily.

1. Rosenstock J et al. *N Engl J Med* 2020;383:2107–16; 2. Lingvay I et al. *Diabetes Care* 2021;4:1595–603; 3. Bajaj H et al. *Diabetes Care* 2021;44:1586–94.