Once weekly insulins
Where are we now?

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Disclosures

CM serves or has served on the advisory panel for Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Imcyse, Insulet, Zealand Pharma, Avotres, Mannkind, Sandoz and Vertex. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for CM from Medtronic, Imcyse, Novo Nordisk, Sanofi and ActoBio Therapeutics; CM serves or has served on the speakers bureau for Novo Nordisk, Sanofi, Eli Lilly and Company, Boehringer Ingelheim, Astra Zeneca and Novartis. Financial compensation for these activities has been received by KU Leuven.

Insulin remains a cornerstone of diabetes treatment

Diabetologia
https://doi.org/10.1007/s00125-021-05568-3

CONSENSUS REPORT

The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

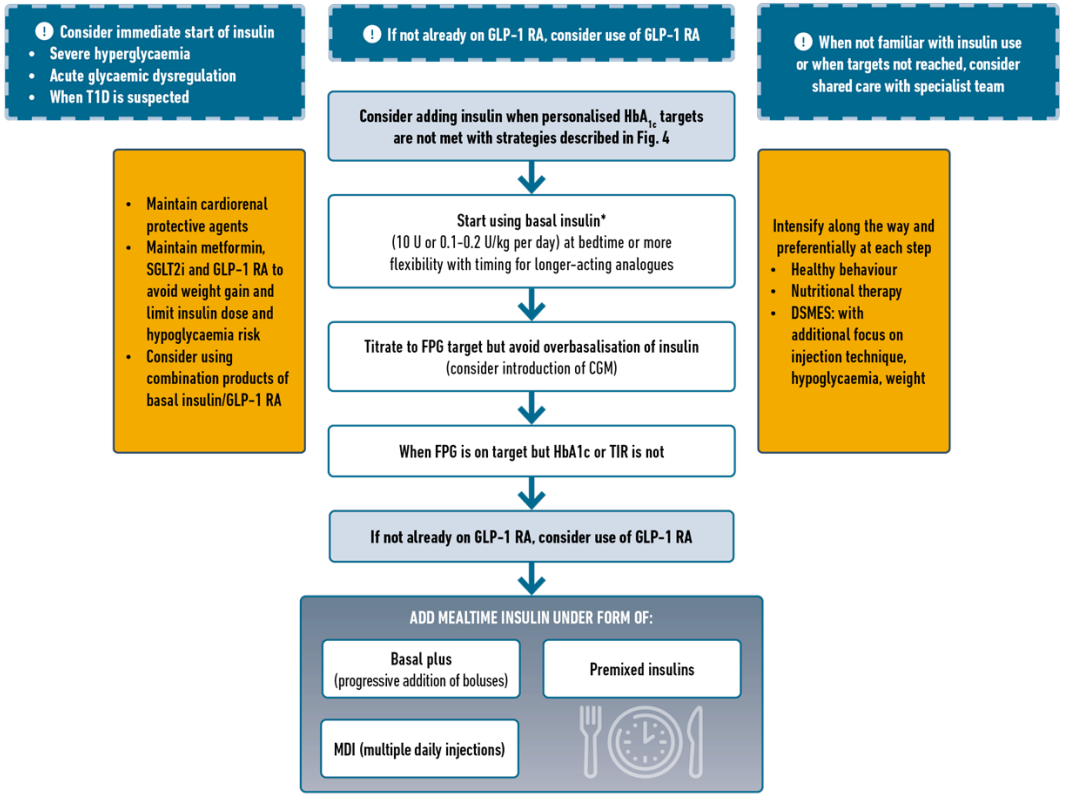
Richard I. G. Holt[1,2] · J. Hans DeVries[3,4] · Amy Hess-Fischl[5] · Irl B. Hirsch[6] · M. Sue Kirkman[7] · Tomasz Klupa[8] · Barbara Ludwig[9] · Kirsten Nørgaard[10,11] · Jeremy Pettus[12] · Eric Renard[13,14] · Jay S. Skyler[15] · Frank J. Snoek[16] · Ruth S. Weinstock[17] · Anne L. Peters[18]

Diabetologia
https://doi.org/10.1007/s00125-022-05787-2

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · Vanita R. Aroda[3] · Billy S. Collins[4] · Robert A. Gabbay[5] · Jennifer Green[6] · Nisa M. Maruthur[7] · Sylvia E. Rosas[8] · Stefano Del Prato[9] · Chantal Mathieu[10] · Geltrude Mingrone[11,12,13] · Peter Rossing[14,15] · Tsvetalina Tankova[16] · Apostolos Tsapas[17,18] · John B. Buse[19]



1. Holt RIG et al Diabetologia/Diabetes Care 2021; 2. Davies MJ et al Diabetologia/Diabetes Care 2022

Insulin remains a cornerstone of diabetes treatment

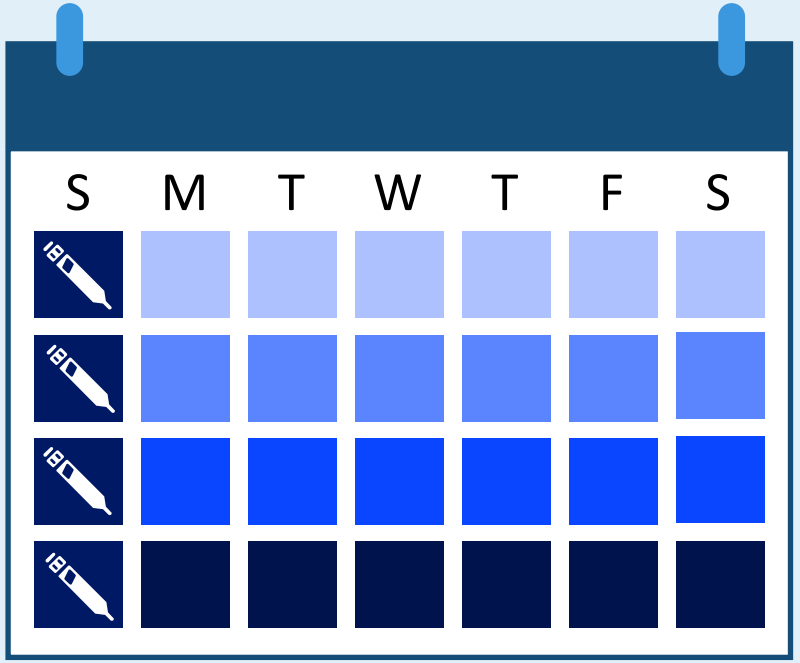
Approximately **537 million people have diabetes** worldwide in 2021, and this is predicted to rise to 783 million by 2045[1]

Up to 40% of people with diabetes (**150–200 million**) globally **require insulin therapy**[2-4]

Due to the progressive nature of diabetes, **many people with T2D** may eventually require and **benefit from insulin therapy**[5]

1. IDF Diabetes Atlas (10th edition). International Diabetes Federation. 2022. http://www.diabetesatlas.org/. Accessed Aug 2022; 2. Garg SK et al. Diabetes Technol Ther 2018;20:1–4; 3. Buse JB. BMJ Open Diab Res Care 2021;9:e002373; 4. Bolli GB et al. Acta Diabetologica 2022; 59:1129–1144; 5. ADA Professional Practice Committee. Diabetes Care. 2022;45(Supplement_1):S125–S143

Recognised attributes of once-weekly medications

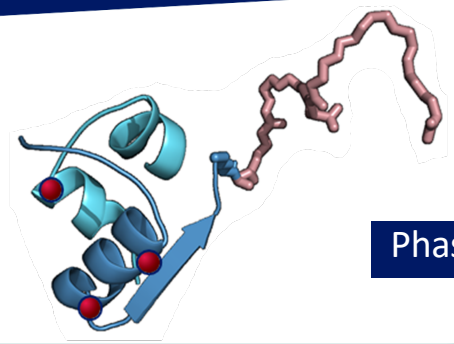


- Greater convenience
- Better medication adherence
- Improved health-related quality of life
- Less overwhelming sense of treatment
- Easier for individuals in need of medical assistance

1. Polonsky WH et al. Diabetes Obes Metab. 2011;13(2):144–14; 2. Polonsky WH et al. Diabetes Ther 2022;13:175–87.

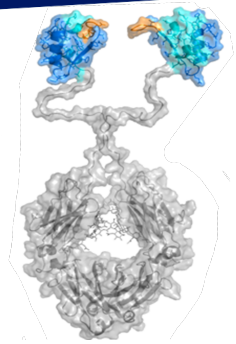
Once-weekly basal insulins in development

Novo Nordisk:
Insulin icodec



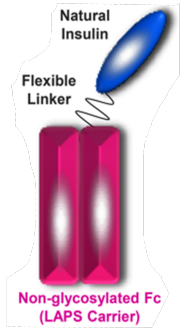
Phase 3

Eli Lilly:
Insulin-Fc



Phase 3

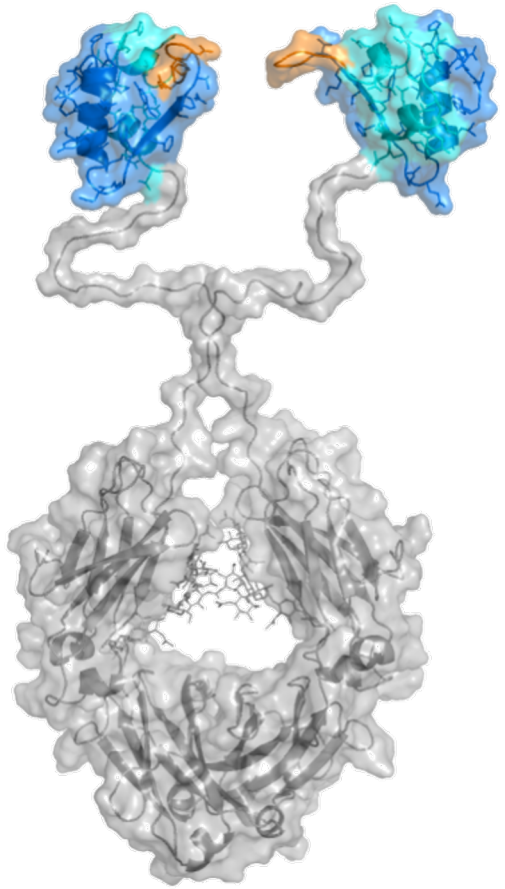
Hanmi:
HM12470



Phase 1

Basal insulin Fc (BIF)- Molecular structure

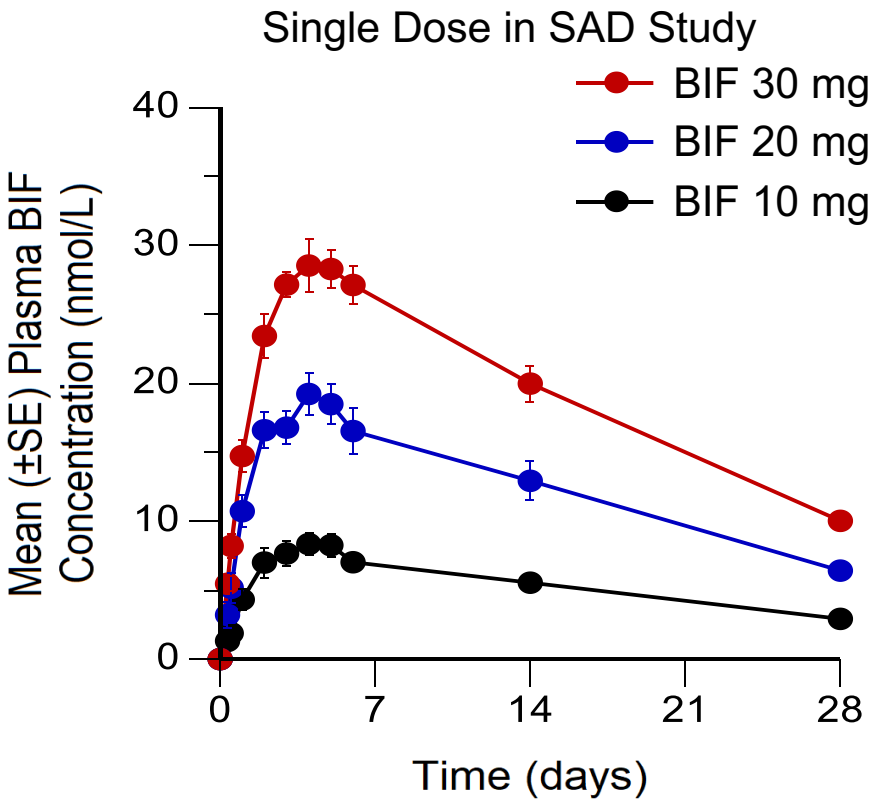
Weekly Basal Insulin Fc (BIF) is a fusion protein that combines a novel single-chain variant of insulin with a human IgG_2 Fc domain.



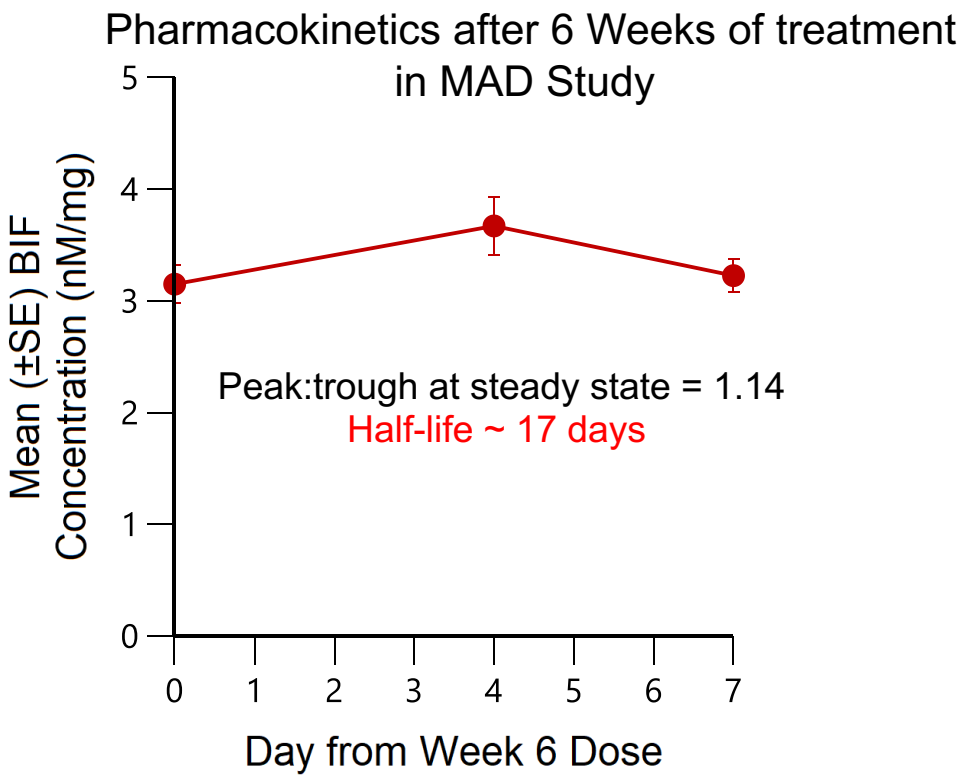
- **Attributes**
- Selective insulin receptor agonist
- Designed for once-weekly SC administration
  - ✓ Reduced affinity for the insulin receptor resulting in low receptor mediated clearance
  - ✓ Large molecule (molecular weight 64.1 kDa) likely with reduced renal clearance
  - ✓ FcRn binding prolongs BIF activity
- Insulin concentration not yet disclosed, but assumed to be considerably higher than 100 U/mL

Heise T *et al. J Endocr Soc* 2021; 5 (Suppl. 1):A329 // Kurtzhals P *et al. Trends Pharmacol Sci* 2021; 42:620-639

Pharmacokinetic profile of BIF allows for once weekly dosing in patients with T2D with a flat peak-to-trough profile



Pharmacokinetics of BIF are dose proportional with low between-day and -subject variability



BIF achieved a low peak:trough ratio on a weekly basis with a total flat insulin profile daily

Heise T *et al. J Endocr Soc* 2021; 5 (Suppl. 1):A329

Basal insulin-Fc phase 2 clinical trials

	32-week titration and switch trial in T2D[1,4]	Switch trial in T1D[2]	Insulin-Fc initiation trial in T2D[3]
Participants	n=399 Basal insulin-treated T2D	n=266 Basal-bolus insulin-treated T1D	n=278 Insulin-naïve T2D
Treatment & trial	Open-label 32 weeks	Open-label 26 weeks	Open-label 26 weeks
	Insulin-Fc algorithm 1 + OADs Insulin-Fc algorithm 2 + OADs Degludec + OADs	Insulin-Fc + bolus insulin Degludec + bolus insulin	Insulin-Fc + OADs Degludec + OADs

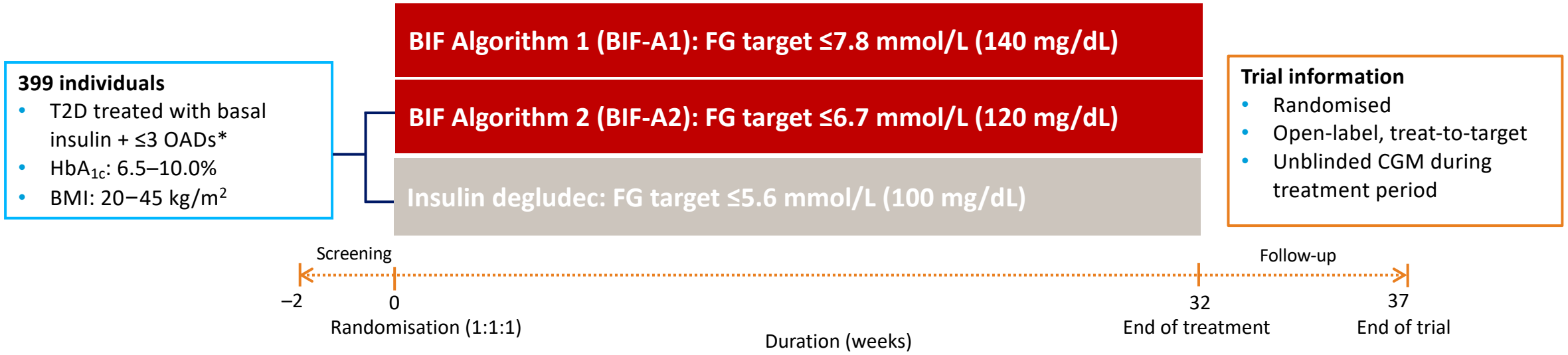
~900 Participants are involved in these insulin-Fc phase 2 trials

Fc, fragment crystallisable region; n, number of participants; OAD, oral antidiabetic drug.

1. Frias JP et al. ENDO 2021. Session OR–09; 2. Frias JP et al . ADA 2022; 3. Bue-Valleskey et al. ADA 2022; 4. Kazda CM et al. ADA 2021

Weekly basal insulin Fc (BIF) Phase 2 programme

BIF basal switch in T2D



Trial objective

To demonstrate BIF is safe and effective in participants with T2D that have already been treated with basal insulin

Primary endpoint

- **Change in HbA_{1c}**

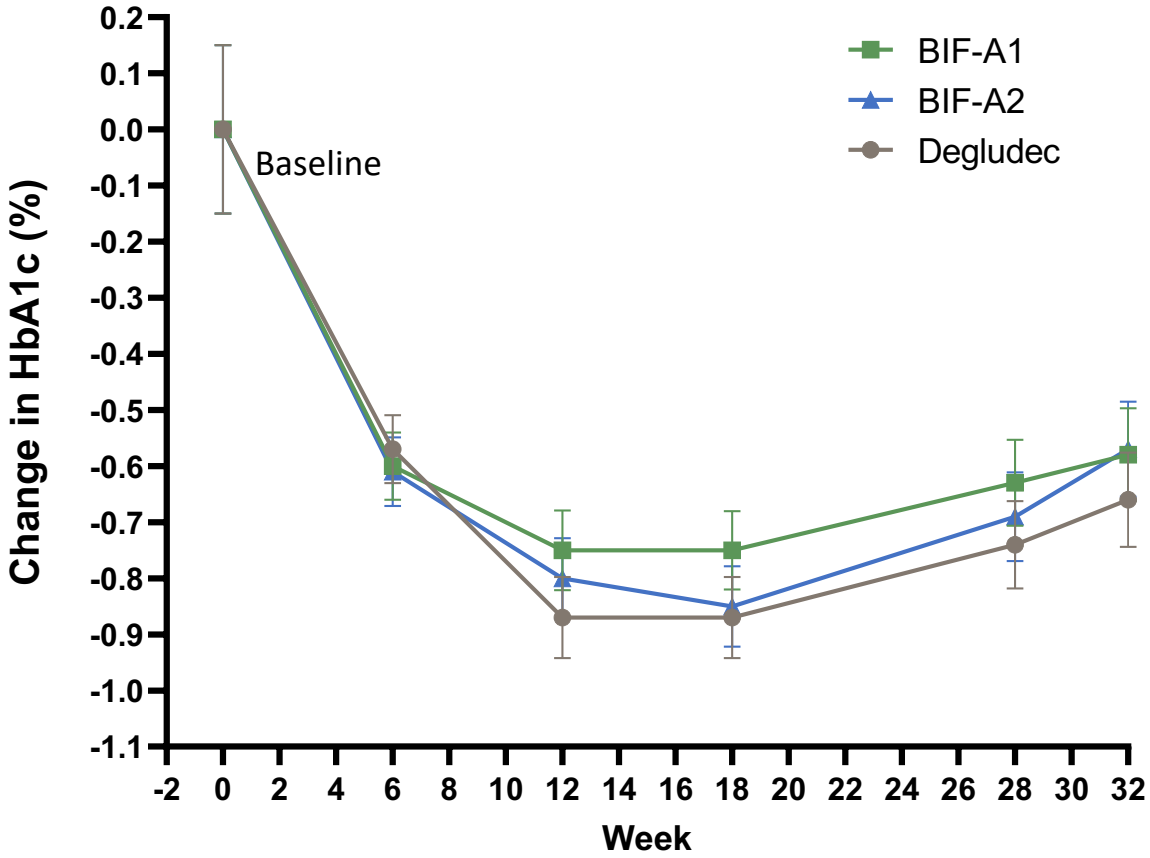
Secondary supportive endpoints

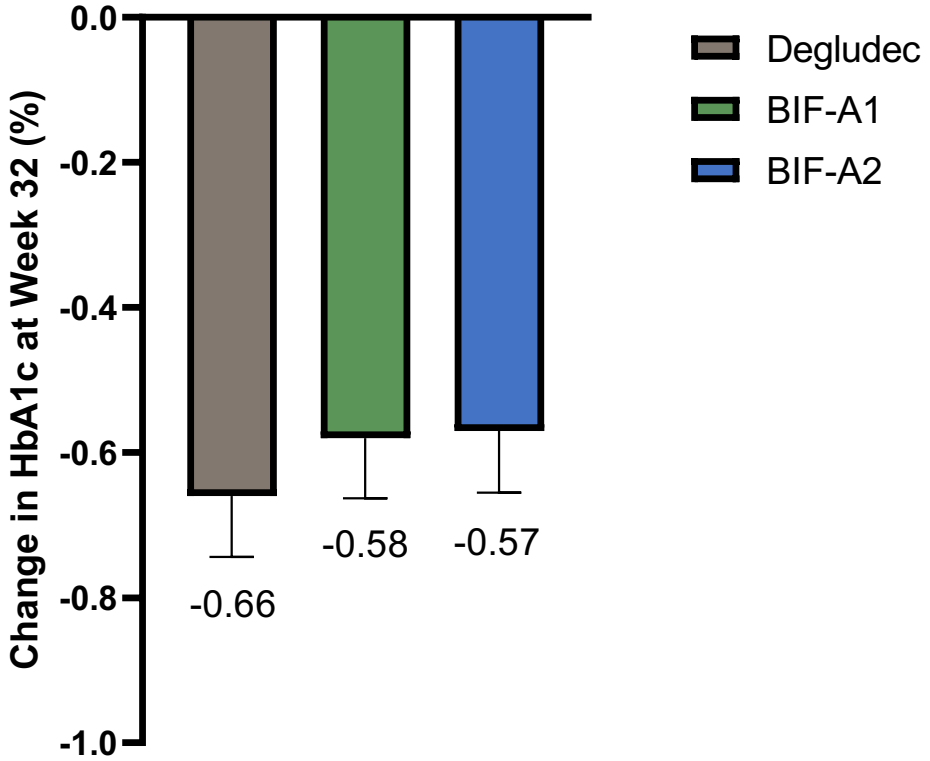
- Changes in FBG, BIF dose, insulin degludec dose, body weight
- Rate of hypoglycaemia

**Dipeptidyl peptidase 4 inhibitor, sodium-glucose co-transporter-2., biguanides, alpha-glucosidase inhibitors, sulfonylureas.*
ClinicalTrials.gov Identifier: NCT03736785.
BMI, body mass index; CGM, continuous glucose monitoring; HbA_{1c}, haemoglobin A1c; FBG, fasting blood glucose; FG, fasting glucose; FPG, fasting plasma glucose; SMBG, self-monitored blood glucose.
Frias JP, et al. J Endocr Soc. 2021 May 3; 5(Suppl 1): A448–A449.

HbA1c

BIF basal switch in T2D



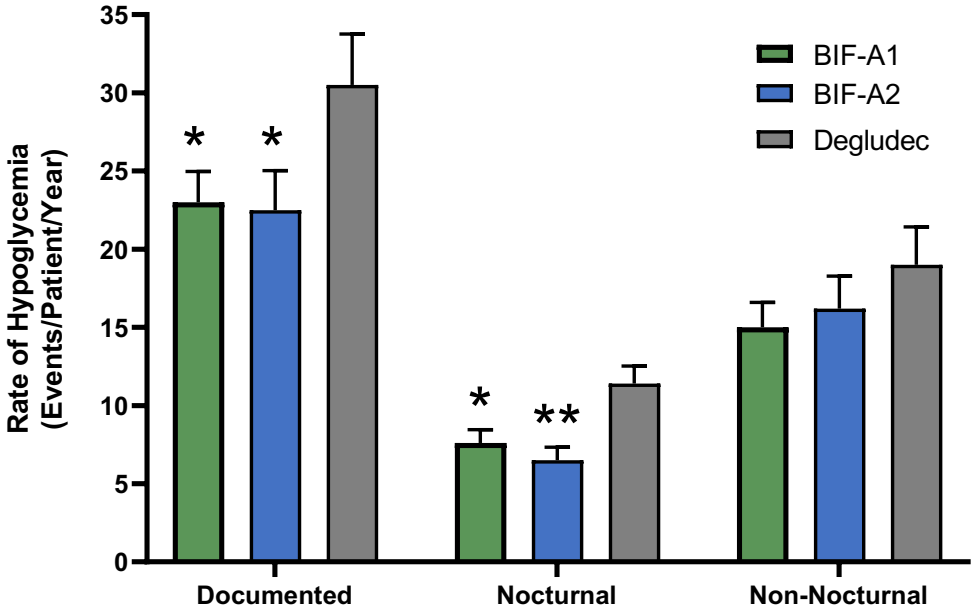


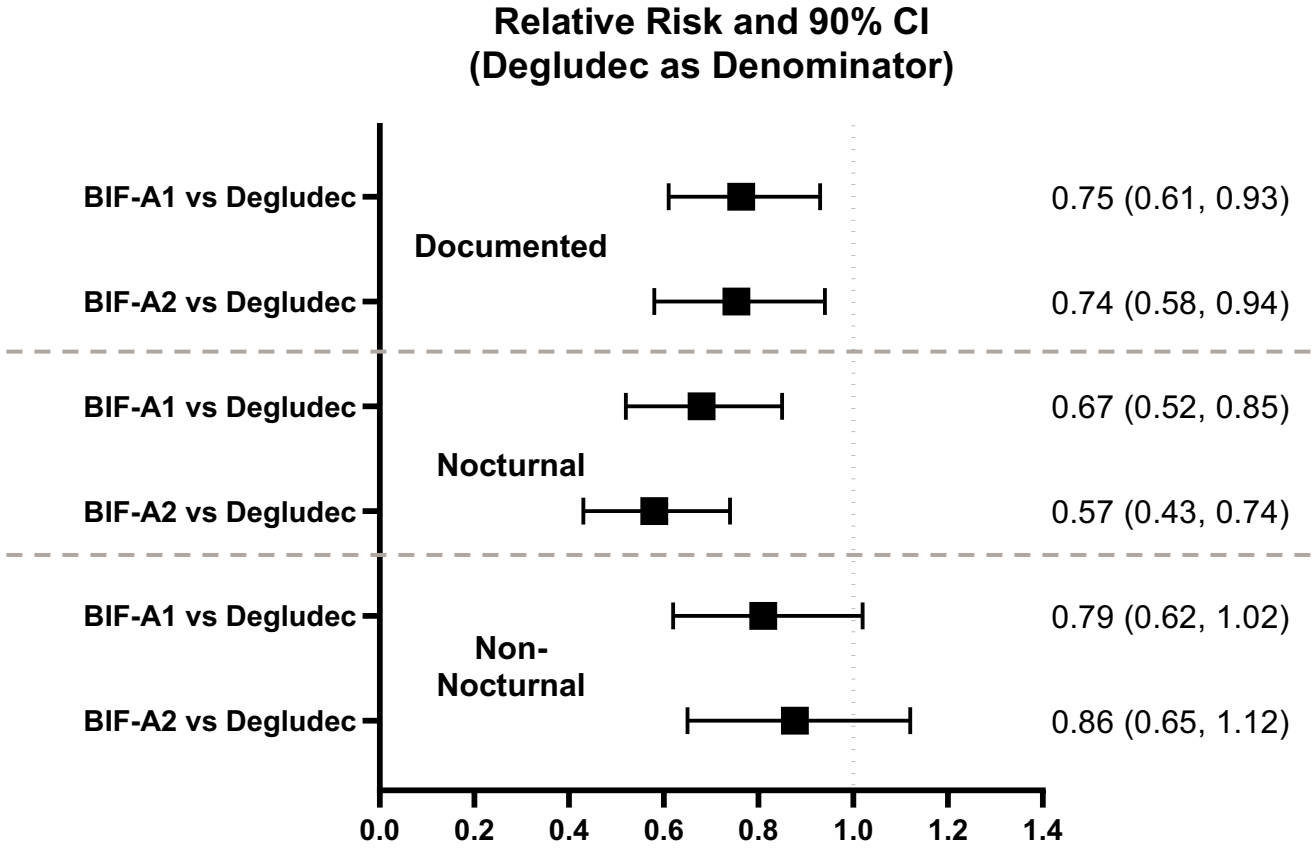
- BIF was noninferior to Degludec for glycemic control as measured by change in HbA1c after 32 weeks (Difference: BIF-A1 - Degludec = 0.08[-0.11,0.28]; BIF-A2 - Degludec 0.09[-0.1, 0.29]
- All treatment groups showed significant improvement from baseline at Week 32 ($p<0.001$)

Frias JP, et al. J Endocr Soc. 2021 May 3; 5(Suppl 1): A448–A449.; Data presented as mean ± SE.

Rate of Hypoglycemia ≤70 mg/dL

BIF basal switch in T2D



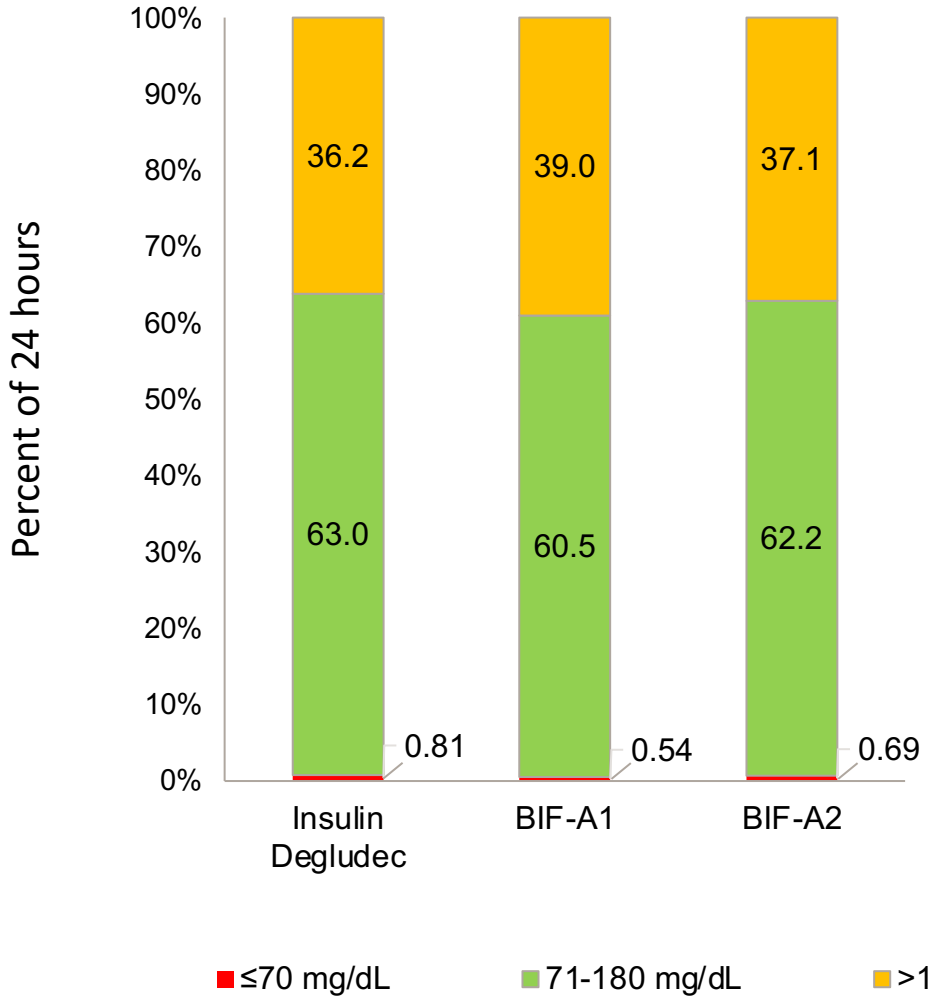


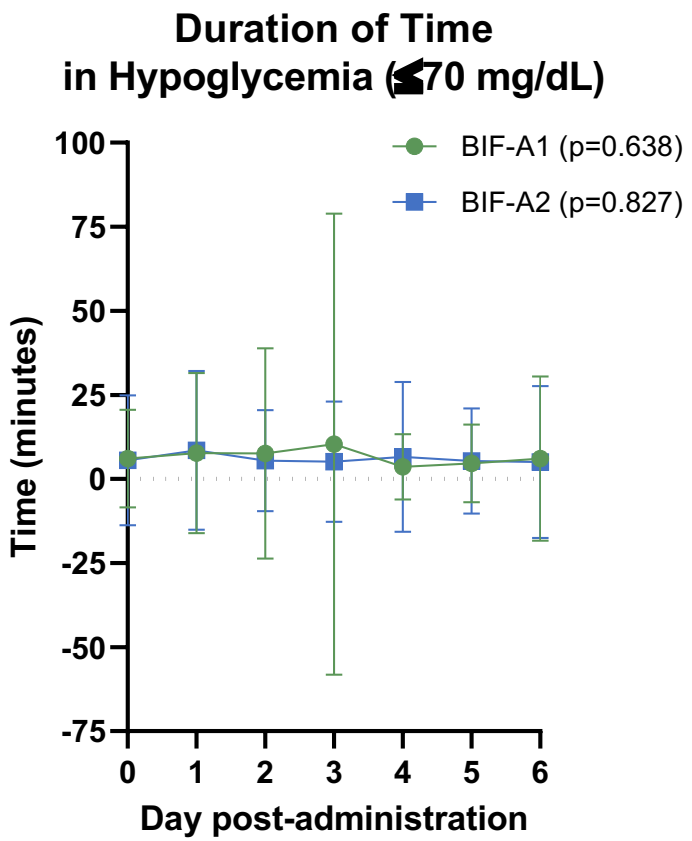
- BIF had a significantly reduced rate of hypoglycemia (≤70 mg/dL) compared to Degludec

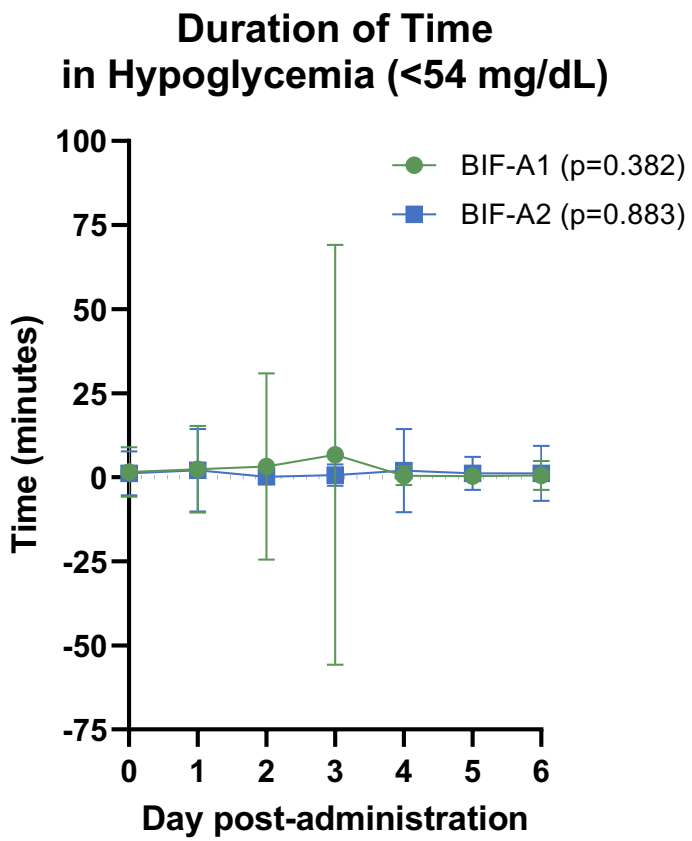
Frias JP, et al. J Endocr Soc. 2021 May 3; 5(Suppl 1): A448–A449.; Data presented as mean ± SE. *p<0.05; **p<0.001

Results from CGM

BIF basal switch in T2D







Kazda CM et al. ADA 2021;

Data presented are the mean percentage of a 24-hour period spent ≤70 mg/dL, 71-180 mg/dL, and >180 mg/dL.

Safety Summary

BIF basal switch in T2D

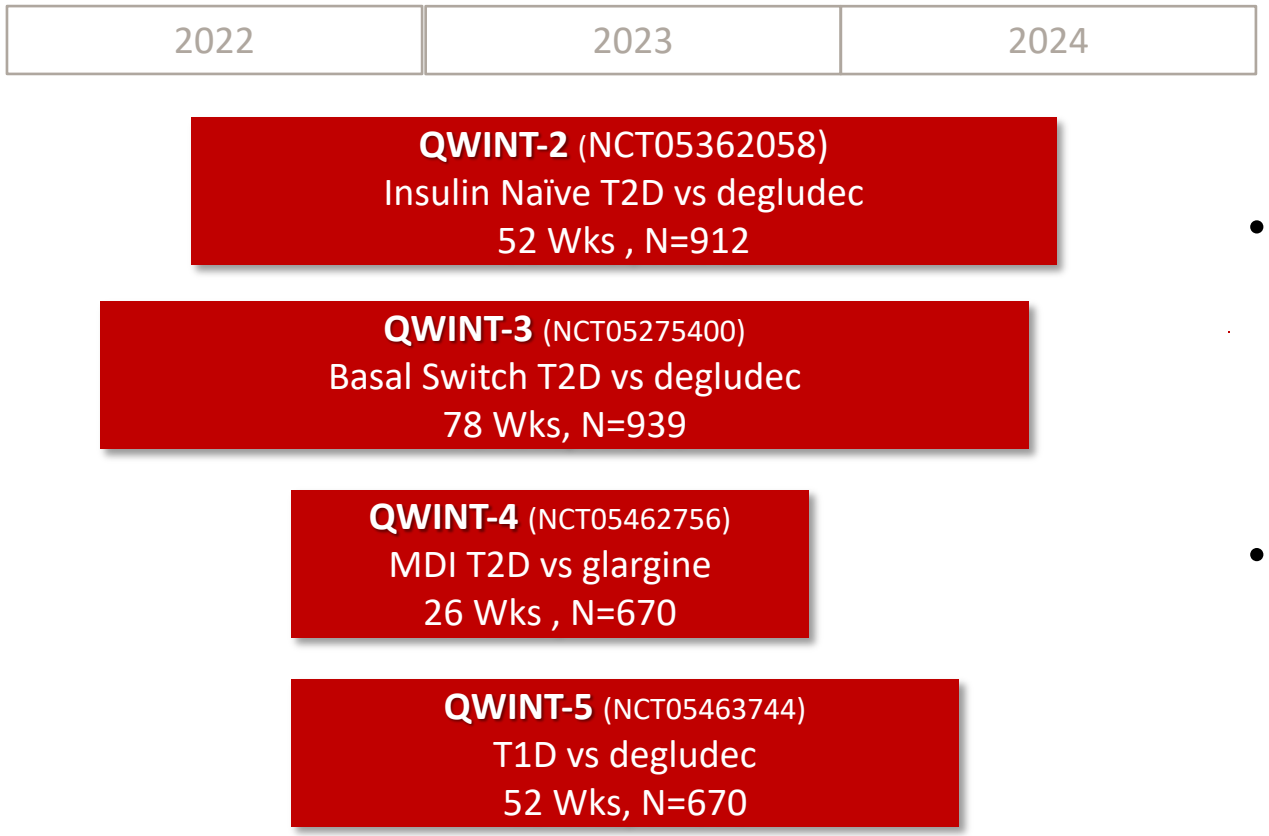
n (%)	Degludec (N=132)	BIF-A1 (N=135)	BIF-A2 (N=131)
Treatment-emergent adverse events	74 (56.1)	79 (58.5)	87 (66.4)
Serious adverse event	10 (7.6)	7 (5.2)	8 (6.1)
Hypoglycemia ≤70 mg/dL (3.9 mmol/L)			
Number of subjects	117 (88.6)	124 (91.9)	117 (89.3)
Number of episodes	2494	1671	1632
Hypoglycemia <54 mg/dL (3.0 mmol/L)			
Number of subjects	76 (57.6)	66 (48.9)	68 (51.9)
Number of episodes	240	174	155
Severe hypoglycemia	0	0	2 (1.5)
Treatment-emergent anti-drug antibodies	1 (0.9)	2 (1.5)	3 (2.3)

Abbreviations: N, number of subjects in the analysis population; n, number of subjects in the specified category.

Frias JP, et al. J Endocr Soc. 2021 May 3; 5(Suppl 1): A448–A449.;

Weekly Basal Insulin Fc (BIF)

Phase 3 Program Initiated In 2022



- The QWINT program consists of five global Phase 3 registration studies in all relevant diabetes populations
  - Details of “QWINT-1” being finalized
- Key endpoints include change from baseline in HbA1c, time in range, and hypoglycemia

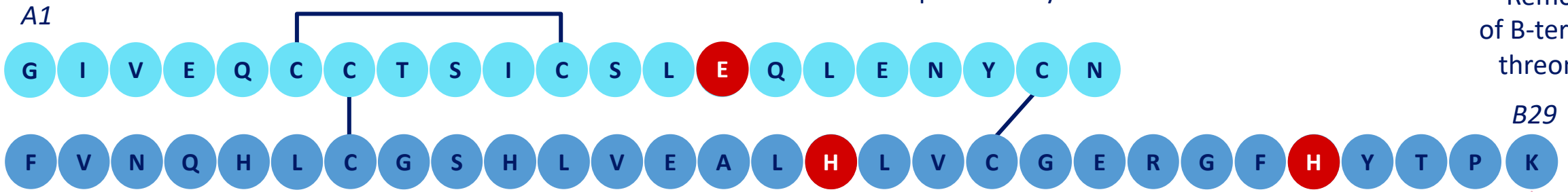
QWINT = QW (once weekly), IN (insulin), T (therapy); T2D = type 2 diabetes; T1D = type 1 diabetes

Slide Courtesy of Rattan Juneja
Eli Lilly and Company

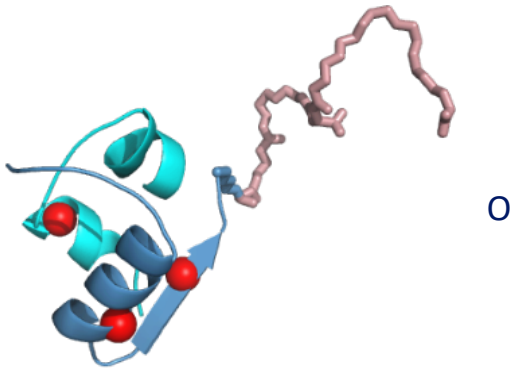
Insulin Icodec: molecular structure

Three amino acid substitutions

- Molecular stability
- Reduced enzymatic degradation
- Low insulin-receptor affinity



Removal of B-terminal threonine



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

C20 icosane fatty diacid

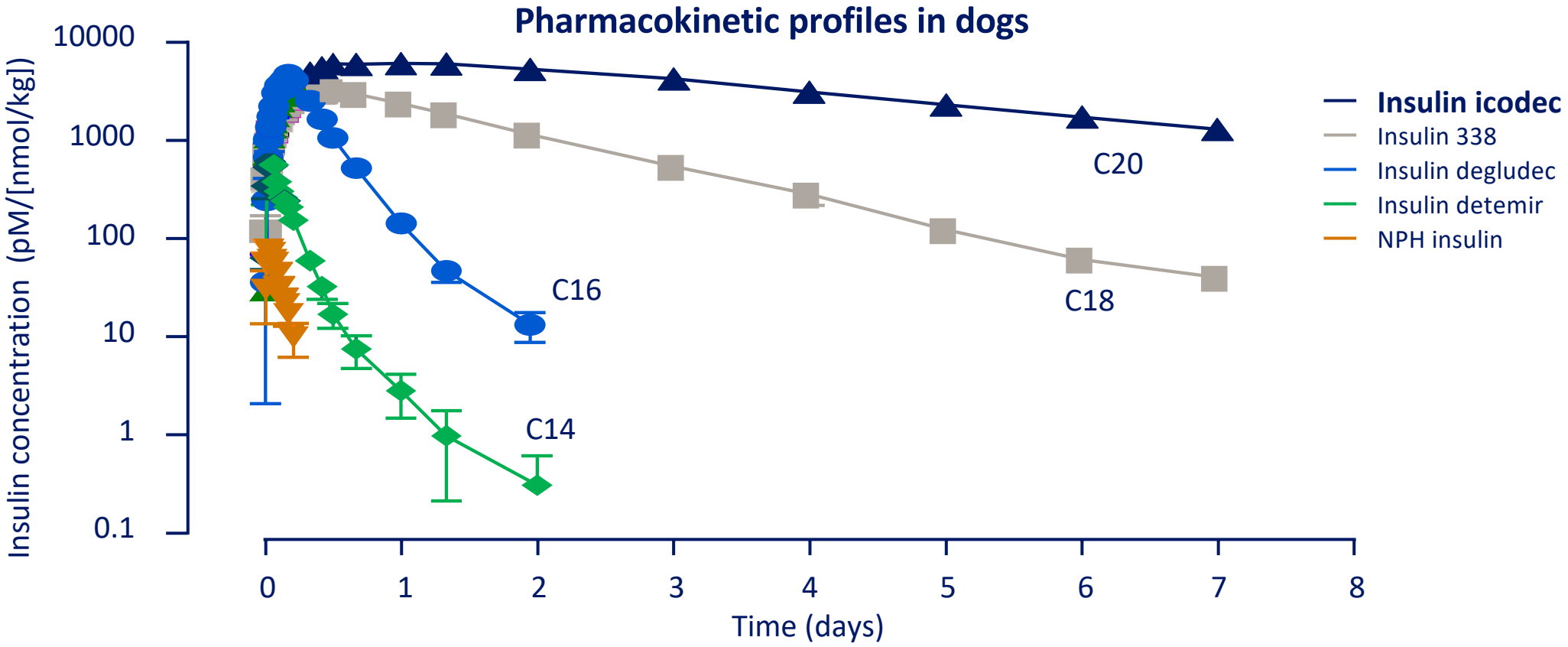
- Strong, reversible binding to albumin
- Reduced receptor-mediated clearance

Half-life ~196 hours (7 days)

Available in a formulation with high concentration (700 U/mL)

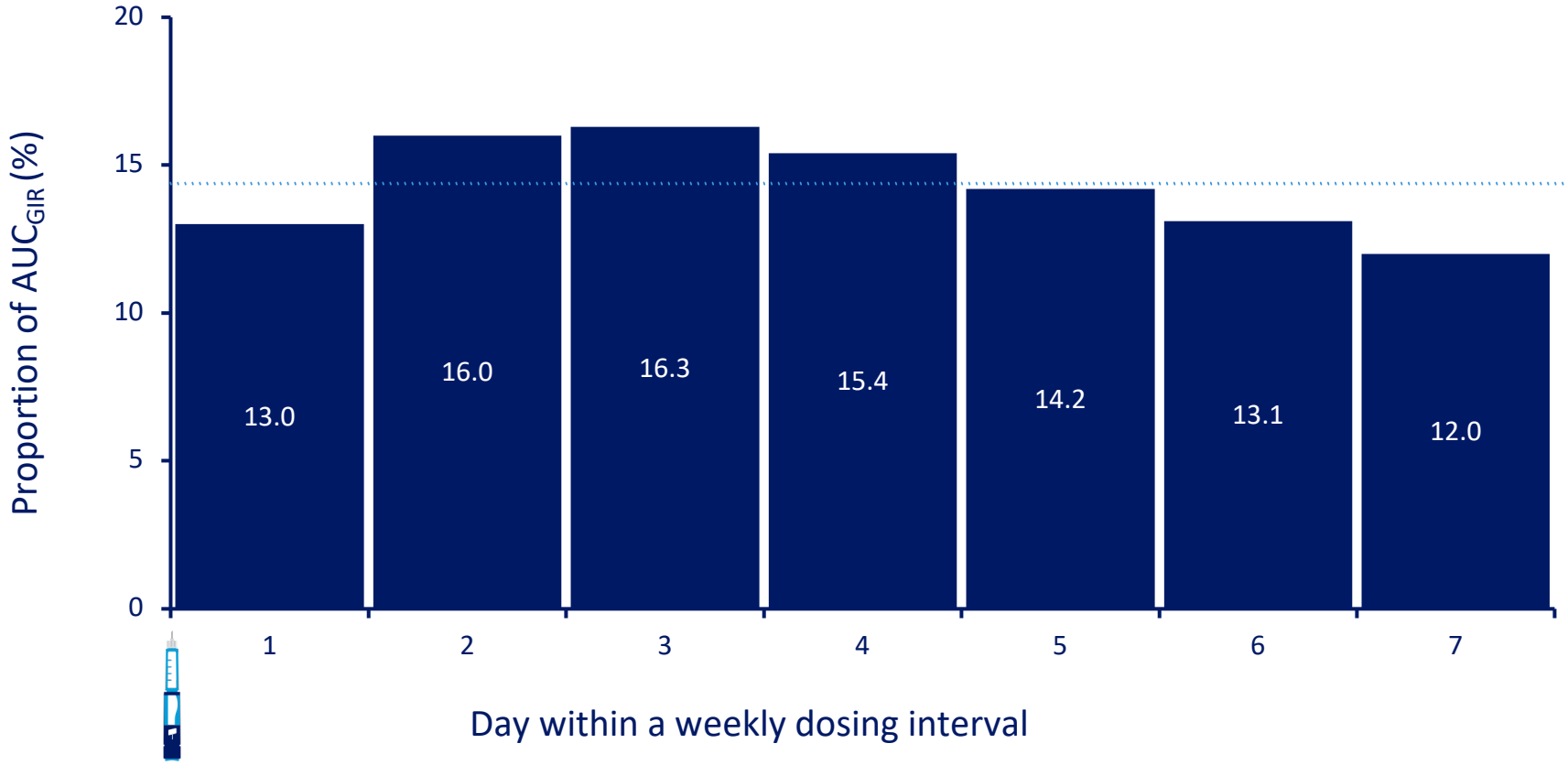
Nishimura E *et al. BMJ Open Diabetes Res Care* 2021; 9:e00230

Acylated basal insulins: Longer fatty-(di-)acid chains promote albumin binding and prolong half-life



Nishimura E *et al. BMJ Open Diabetes Res Care* 2021 Aug;9(1):e00230

Insulin icodec: Distribution of the glucose-lowering effect over one week at steady-state (modelled data)



Dotted line represents equal distribution across 7 days (14.3%)

Nishimura E *et al. BMJ Open Diabetes Res Care* 2021 Aug;9(1):e00230

Icodec phase 2 clinical trials

Icodec in insulin-naïve T2D[1]
(NN1436-4383)

- Icodec + OADs
- Glargine U100 + OADs

American Diabetes Association. 80TH SCIENTIFIC SESSIONS
A VIRTUAL EXPERIENCE
June 12-16, 2020

EASD VIRTUAL MEETING AI
Join us online 21-25 September 2020
easd.org/virtualmeeting

The NEW ENGLAND JOURNAL of MEDICINE

Icodec titration trial in insulin-naïve T2D[2]
(NN1436-4465)

- Icodec titration A
- Icodec titration B
- Icodec titration C
- Glargine U100

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easd.org/virtualmeeting

Diabetes Care

Switching from daily basal insulin to icodec in T2D[3]
(NN1436-4466)

- Icodec with loading dose
- Icodec without loading dose
- Glargine U100

EASD VIRTUAL MEETING AI
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Diabetes Care

600 subjects were involved in these icodec trials

OADs, oral antidiabetic drugs

1. Rosenstock J et al. N Engl J Med. 2020;383:2107–2116; 2. Lingvay I et al. Diabetes Care. 2021;44(7):1595–1603; 3. 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

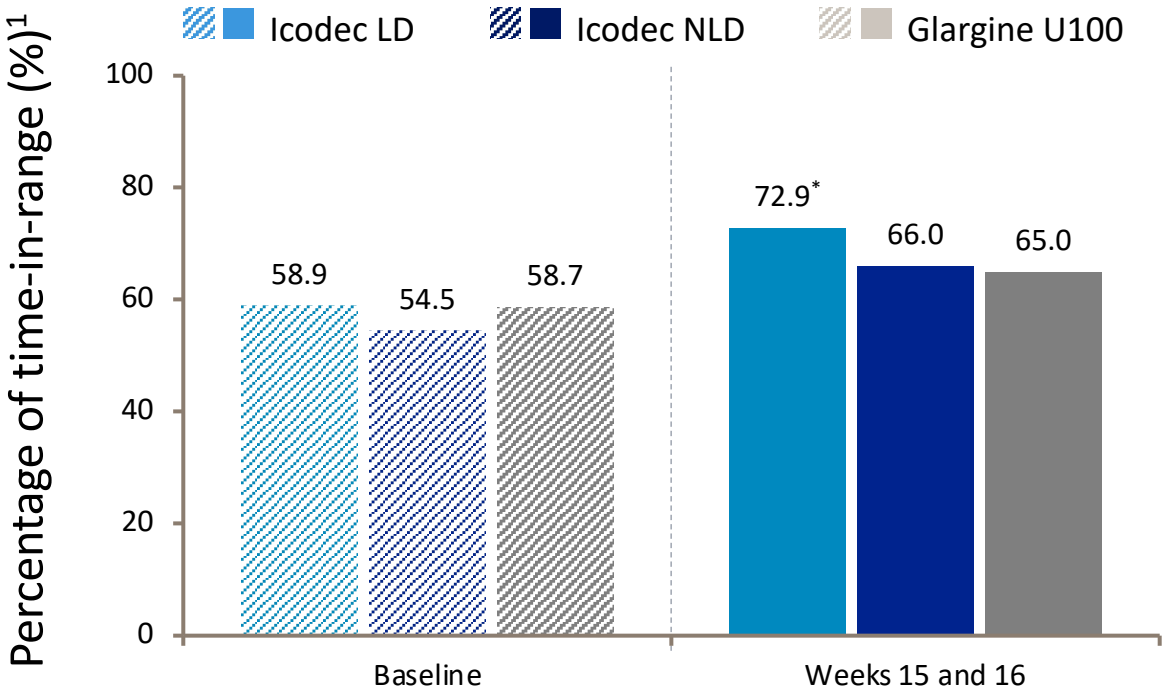
**OD or BID basal insulin/insulin glargine U300.*

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).

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



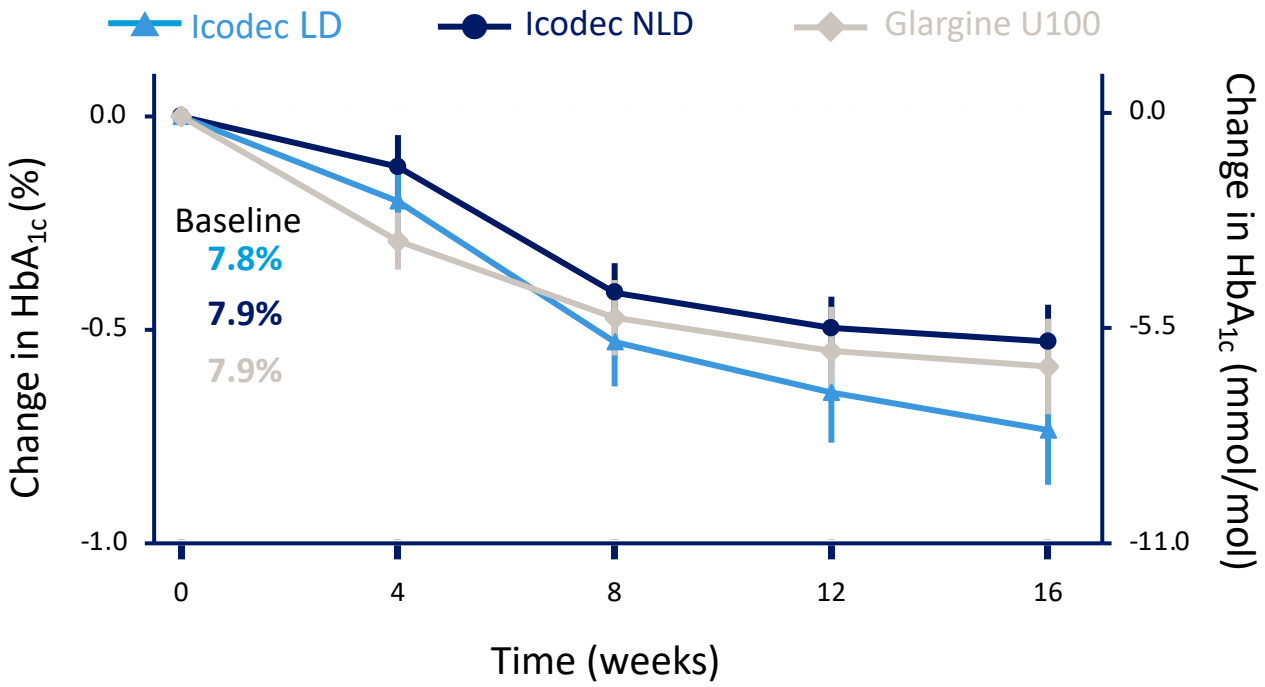
$TIR_{3.9–10.0\ mmol/L\ (70–180\ mg/dL)}$, weeks 15 & 16

	ETD vs. glargine U100	
	ETD (%)	**95% CI**
Icodec LD	7.88	[1.83; 13.93]*
Icodec NLD	1.01	[–5.33; 7.5]

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

HbA1c

Switching from OD/BID basal insulin to OW icodec



	Estimated mean change from baseline to week 16 (%)	ETD vs. glargine U100	
		ETD (%)	95% CI
Icodec LD	–0.8	–0.23	[–0.49; 0.02]
Icodec NLD	–0.5	0.07	[–0.19; 0.33]
Glargine U100	–0.5	–	

Full analysis set. Observed data are mean ± standard error to the mean. Estimated mean values and the corresponding CIs at week 16 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.
Bajaj H et al. Diabetes Care. 2021; 44(7):1586–1594.

Hypoglycaemic episodes
Switching from OD/BID basal insulin to OW icodec

	Icodec **LD** (n=54)				Icodec **NLD** (n=50)				Glargine U100 (n=50)			
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
Level 1	19	(35.2)	83	3.81	26	(52.0)	87	4.29	22	(44.0)	76	3.77
Level 2 + Level 3	4	(**7.4**)	17	0.78	2	(**4.0**)	3	0.15	6	(**12.0**)	16	0.79
Level 3	0	–	–	–	0	–	–	–	0	–	–	–

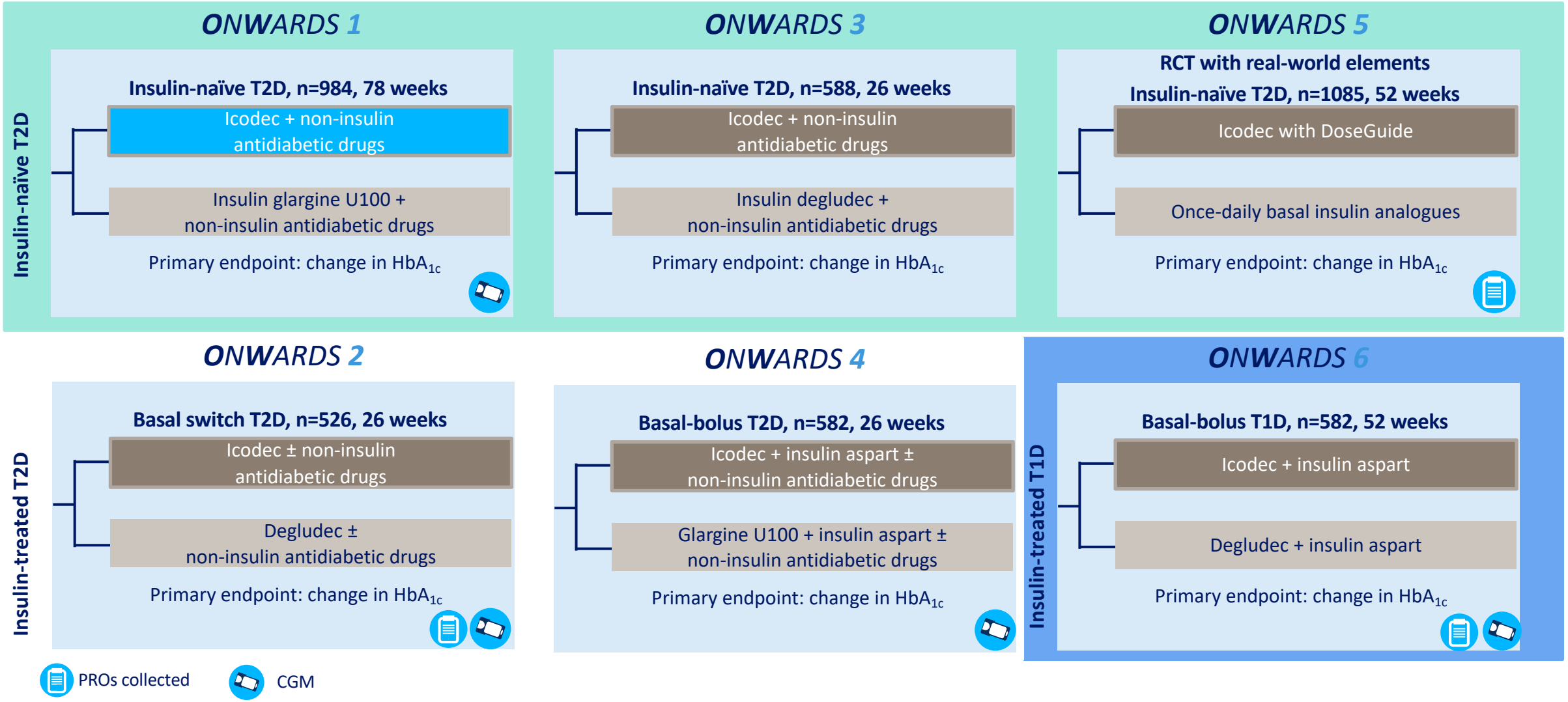
Safety analysis set. Hypoglycaemia alert value (level 1): plasma glucose value of <3.9 mmol/L (<70 mg/dL) and ≥3.0 mmol/L (≥54 mg/dL) confirmed by BG meter. Clinically significant hypoglycaemia (level 2): plasma glucose value of <3.0 mmol/L (<54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. %, percentage of patients with one or more events; BG, blood glucose; BID, twice-daily; E, number of events; LD, loading dose; N, number of patients with one or more events; n, number of subjects; NLD, no loading dose;
OD, once-daily; OW, once-weekly; R, rate (number of events per patient-year of exposure).
1. Bajaj H et al. Diabetes Care. 2021; 44(7):1586–1594.

Hypoglycaemic episodes
Switching from OD/BID basal insulin to OW icodec

	Icodec **LD** (n=54)				Icodec **NLD** (n=50)				Glargine U100 (n=50)			
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
Level 1	19	(35.2)	83	3.81	26	(52.0)	87	4.29	22	(44.0)	76	3.77
Level 2 + Level 3	4	(7.4)	17	**0.78**	2	(4.0)	3	**0.15**	6	(12.0)	16	**0.79**
Level 3	0	–	–	–	0	–	–	–	0	–	–	–

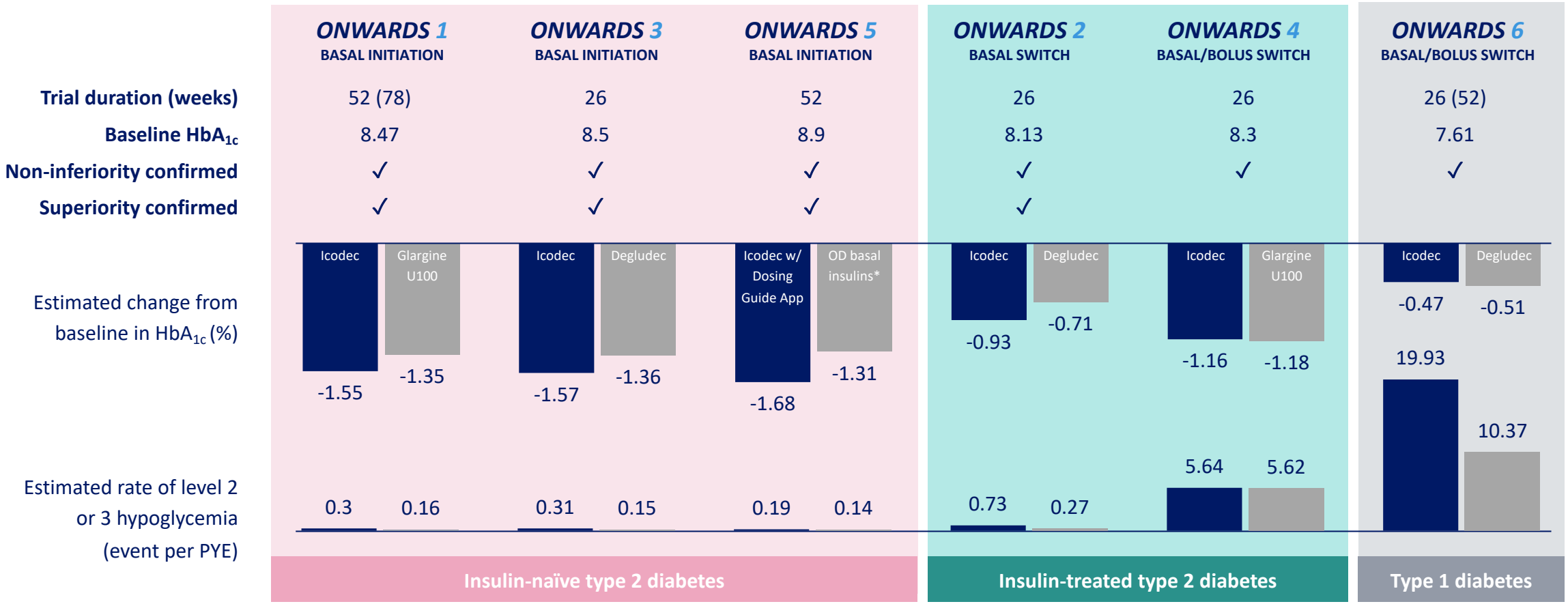
Safety analysis set. Hypoglycaemia alert value (level 1): plasma glucose value of <3.9 mmol/L (<70 mg/dL) and ≥3.0 mmol/L (≥54 mg/dL) confirmed by BG meter. Clinically significant hypoglycaemia (level 2): plasma glucose value of <3.0 mmol/L (<54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. %, percentage of patients with one or more events; BG, blood glucose; BID, twice-daily; E, number of events; LD, loading dose; N, number of patients with one or more events; n, number of subjects; NLD, no loading dose;
OD, once-daily; OW, once-weekly; R, rate (number of events per patient-year of exposure).
1. Bajaj H et al. Diabetes Care. 2021; 44(7):1586–1594.

Weekly ICODEC
Phase 3 Program initiated in 2021



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

ONWARDS programme: topline results



*insulin degludec or insulin glargine U100/U300

1. Novo Nordisk A/S company announcement, 28 April 2022; 2. Novo Nordisk A/S company announcement, 3 June 2022; 3. Novo Nordisk A/S company announcement, 29 July 2022. 3. Novo Nordisk A/S company announcement, 3 October 2022. Clinically significant hypoglycemia (level 2): blood glucose <3.0 mmol/L (<54 mg/dL) confirmed by blood glucose meter. Severe hypoglycemia (level 3): hypoglycemia with severe cognitive impairment requiring external assistance for recovery. OD, once-daily; RCT, randomized clinical trial.

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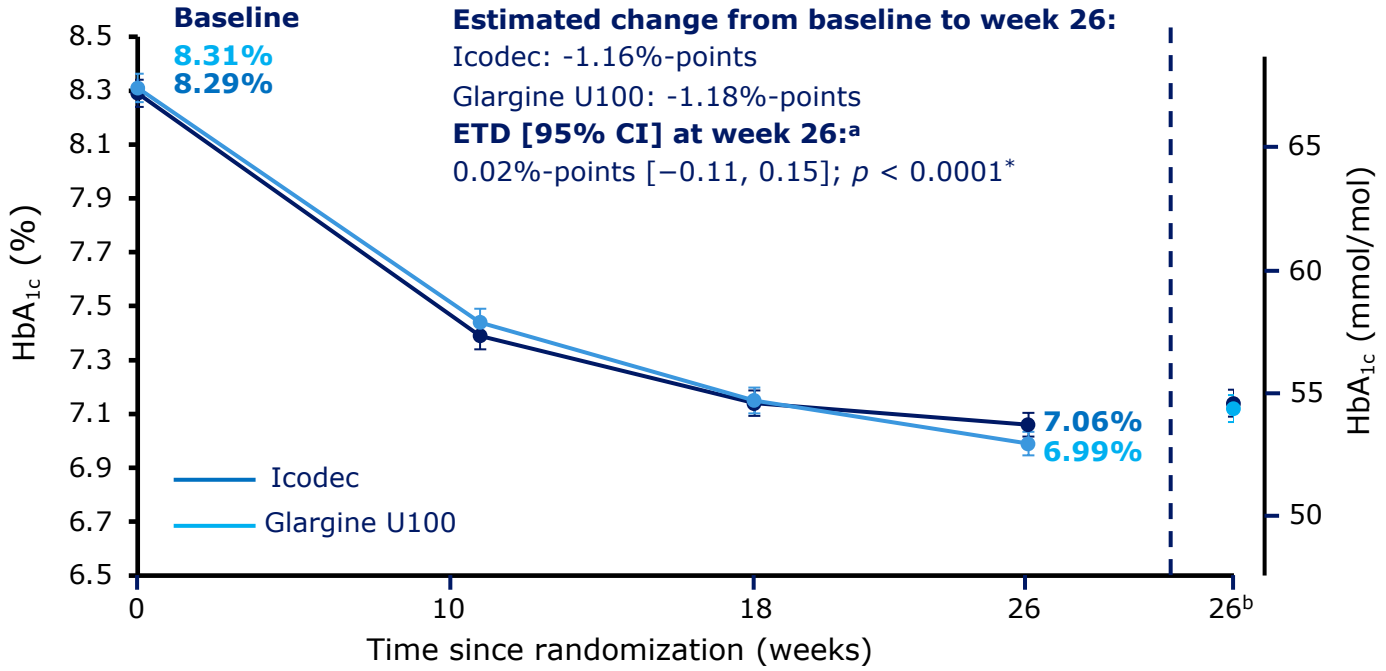
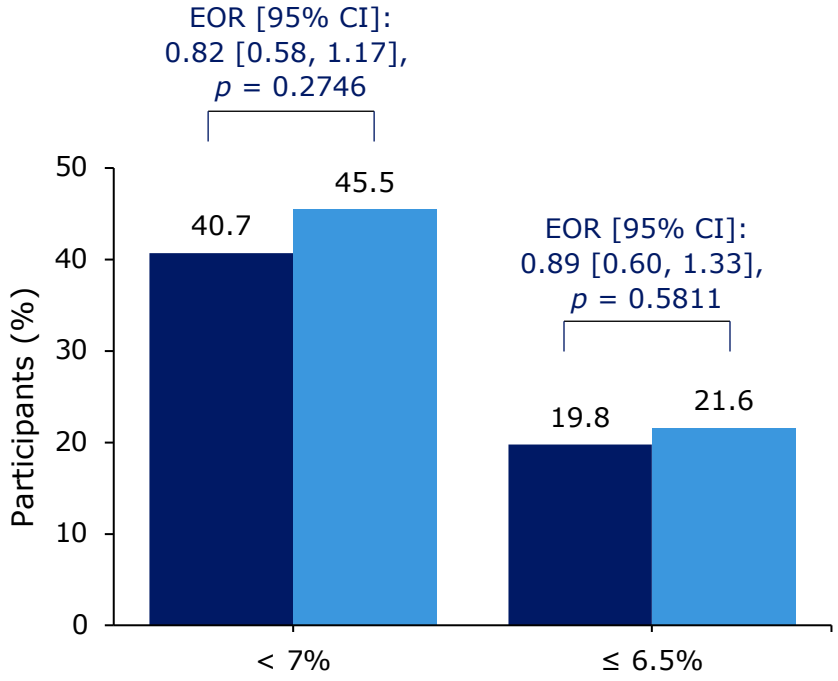
ONWARDS 4

BASAL/BOLUS SWITCH

Primary endpoint: change in HbA_{1c} from baseline to week 26





- From baseline to week 26, the estimated change in body weight was +2.73 kg (icodec) vs +2.16 kg (glargine U100) (ETR [95% CI]: 0.57 [-0.39, 1.54], p = 0.2444)

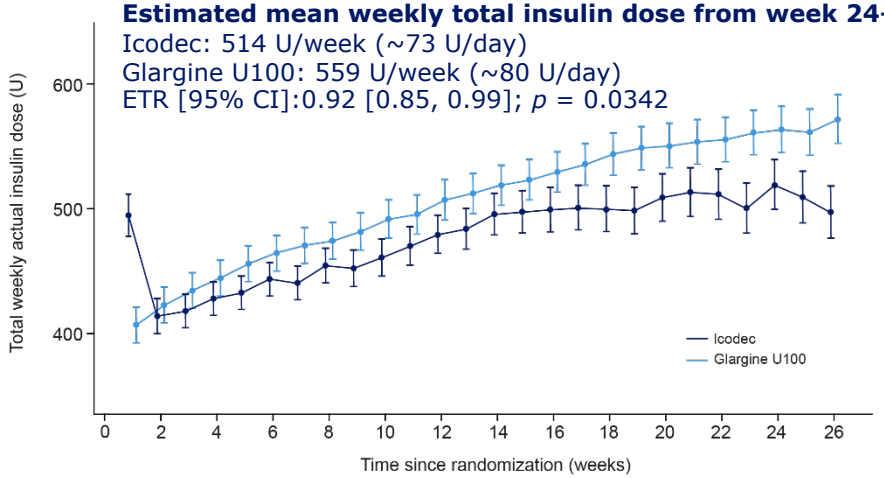
Line graph shows mean HbA_{1c} levels over time among participants who received once-weekly icodec and once-daily glargine U100. Graph shows mean ± standard error of the mean (error bars).
*P value for the test of non-inferiority (0·3%-point margin) of icodec versus glargine U100 (non-inferiority confirmed). [a]Value is the estimated difference between the groups (icodec-glargine U100). [b]Data shown at week 26 are the estimated mean values and the corresponding standard error at week 26 based on multiple imputations. Bar graph shows the estimated percentages of participants who had attained a HbA_{1c} level of <7% or ≤6·5% after 26 weeks in the full analysis set. The binary response after 26 weeks is analyzed using a binary logistic regression model (logit link) with treatment, region and personal CGM device use as fixed factors, and the baseline HbA_{1c} value as covariate.
CGM, continuous glucose monitoring; CI, confidence interval; EOR, estimated odds ratio; ETD, estimated treatment difference (icodec-glargine U100); ETR, estimated treatment ratio (glargine, insulin glargine; HbA_{1c}, glycated hemoglobin; icodec, insulin icodec

ONWARDS 4

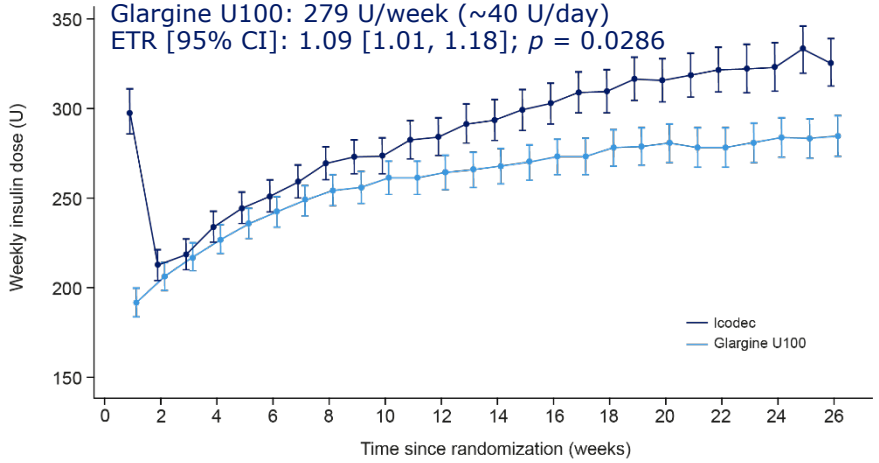
BASAL/BOLUS SWITCH

Weekly total insulin dose

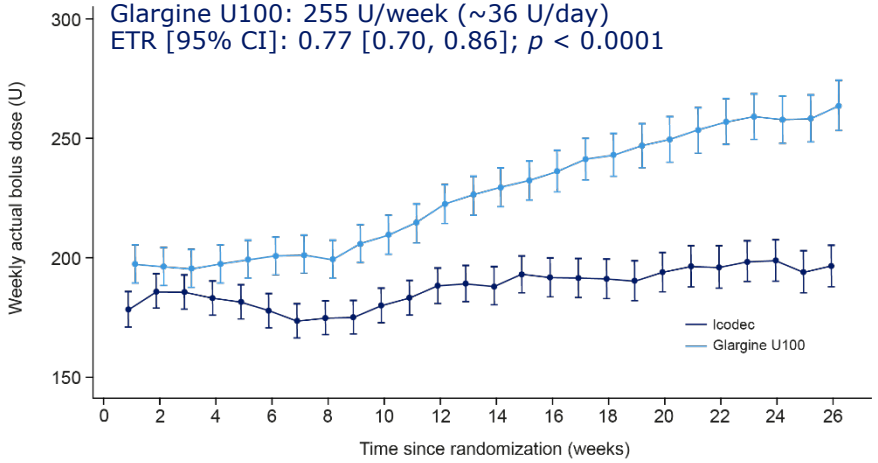
Estimated mean weekly total insulin dose from week 24–26:
Icodec: 514 U/week (~73 U/day)
Glargine U100: 559 U/week (~80 U/day)
ETR [95% CI]:0.92 [0.85, 0.99]; p = 0.0342



Estimated mean weekly total basal insulin dose from week 24–26:
Icodec: 305 U/week (~44 U/day)
Glargine U100: 279 U/week (~40 U/day)
ETR [95% CI]: 1.09 [1.01, 1.18]; p = 0.0286



Estimated mean weekly total bolus insulin dose from week 24–26:
Icodec: 197 U/week (~28 U/day)
Glargine U100: 255 U/week (~36 U/day)
ETR [95% CI]: 0.77 [0.70, 0.86]; p < 0.0001



Line graphs show the observed mean weekly total insulin dose, the total basal component of total insulin dose and the total bolus component of total insulin dose in U/week in the SAS. These insulin doses were also calculated as U/day. The log-transformed response from week 24 to week 26 was analysed using an ANCOVA model with treatment, region and personal CGM device use as fixed factors, and log-transformed screening response as covariate.
ANCOVA, analysis of covariance; CI, confidence interval; ETR, estimated treatment ratio; SAS, safety analysis set; U, units

ONWARDS 4

BASAL/BOLUS SWITCH

Overall hypoglycemic episodes

On-treatment period[a]

Overall hypoglycemic episodes	Icodec (n = 291)		Glargine U100 (n =291)		ERR for icodec vs glargine U100 [95% CI]
	n (%)	E (R)	n (%)	E (R)	
Clinically significant (level 2) hypoglycemia[b]	148 (50.9)	937 (5.59)	160 (55.0)	935 (5.61)	0.99 [0.73, 1.34], p = 0.927
Severe (level 3) hypoglycemia[c]	4 (1.4)	7 (0.04)	2 (0.7)	3 (0.02)	2.19 [0.20, 24.44], p = 0.525
Combined clinically significant (level 2)[b] or severe (level 3)[c] hypoglycaemia	150 (51.5)	944 (5.64)	162 (55.7)	938 (5.62)	0.99 [0.73, 1.33], p = 0.929

- Overall, 58.8% (icodec) and 57.4% (glargine U100) of participants experienced an adverse event
- Three deaths were reported (two in the icodec arm; one in the glargine arm); all of which were assessed as unlikely to be related to trial drug
- No new safety issues were identified in relation to icodec in this trial

All values measured by the blood glucose meter indicative of hypoglycemia were recorded as hypoglycemic episodes, irrespective of the reason for measurement.
[a]In the 'on-treatment period' in the SAS. The 'on-treatment period' represents the time during which participants were considered to be exposed to treatment. This is defined as the time from first dose of trial treatment to: the follow-up visit; the last date on product (plus 5 weeks for once-daily insulin or plus 6 weeks for once-weekly insulin); or the end date for the in-trial observation period. [b]Clinically significant hypoglycemia (level 2): blood glucose < 54 mg/dL, confirmed by blood glucose meter. [c]Severe hypoglycemia (level 3): hypoglycemia with severe cognitive impairment requiring external assistance for recovery.
CI, confidence interval; E, number of events; ERR, estimated rate ratio; glargine, insulin glargine; icodec, insulin icodec; PYE, patient years of exposure; R, rate (number of events per PYE); SAS, safety analysis set

Summary and conclusions

In people with T2D, phase 2 (BIF and ICODEC) indicate that novel once weekly insulins offer:

- Similar/better HbA1c lowering and similar/better TIR to once daily basal insulins (insulin-naïve, basal insulin switch, MDI)
- Hypoglycemia rates were comparable, without increase in severe hypoglycemia