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

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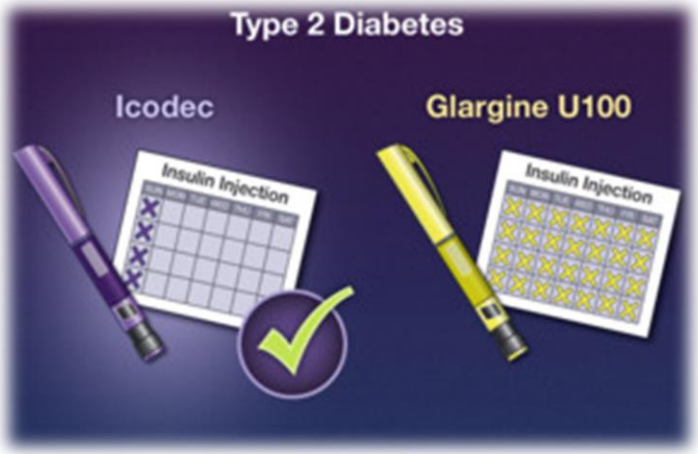
Objective of this study:



This article takes a critical look at the phase 3a study which compares the efficacy and safety of insulin icodec administered once a week, to those of basal insulin glargine (100 units/mL [U100]) injected daily in individuals with long-standing type 2 diabetes on a basal-bolus regimen.

Introduction :

a basal-bolus regimen (which is Basal insulin (Lantus) intensificated by the addition of Bolus insulin(NovoRapid/Humalog)before each main meal is often required to attain and maintain adequate glycaemic control.

but the frequency of injection, and patient perceptions of the effect of their treatment on daily activities often lead to delayed insulin intensification or reduced adherence to the prescribed treatment regimen.

• Insulin Icodec (icodec):

Is a novel basal insulin analogue under development for the treatment of diabetes has the advantage of **having a half-life of approximately seven days** and allow peak **blood concentrations to be reached 16 hours after injection**.

This modified insulin molecule binds to albumin and creates circulating complexes with an elimination half-life of approximately 196 hours.

Its profile pharmacokinetics which makes weekly administration possible, reducing the number of injections and improving potentially the acceptability of treatment by patients.

Because It' s proved that :

Reducing the frequency of insulin injections might reduce the treatment burden for individuals with type 2 diabetes, which could lead to increased treatment persistence and adherence resulting in improved glycaemic control.

Methods :

this was a phase 3a randomised, open-label, active-controlled, multicentre, multinational (in nine countries : Belgium, India, Italy, Japan, Mexico, the Netherlands, Romania, Russia and the USA) treat to target non inferiority trial.

Period of the trial :

"between May 14 and Oct 29, 2021"

The trial involved a 2-week screening period, a 26-week randomised treatment period, and a 5-week follow-up period

Eligible participants :

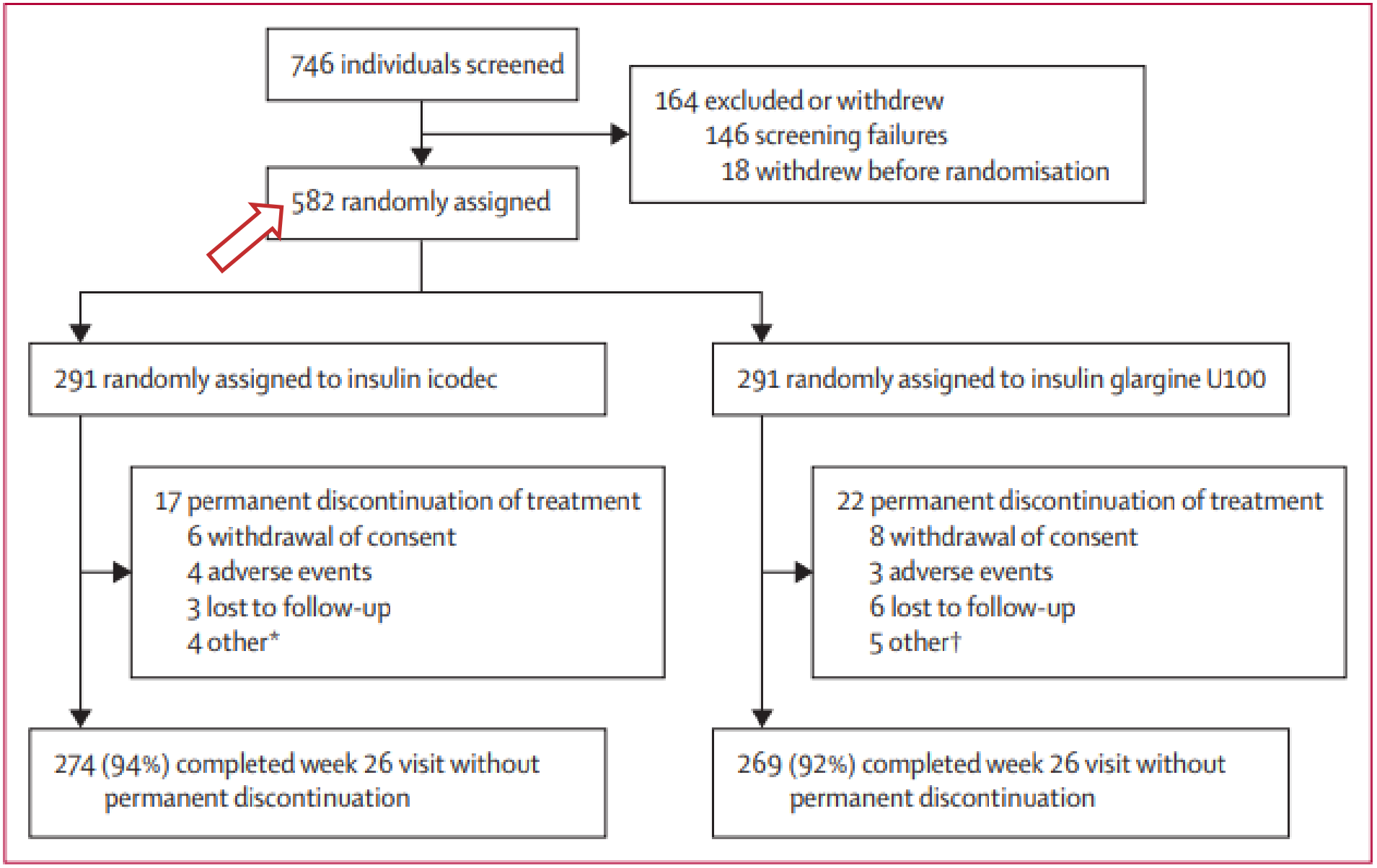
"582 (78%) were included in the trial"

Aged ≥18 years with inadequately controlled type 2 diabetes had an HbA1c of 7–10% (53–86 mmol/mol) and who have been on a basal-bolus regimen (including once-daily injections of basal insulin and two to four daily injections of bolus insulin) with or without non-insulin glucose-lowering medications for at least 90 days before screening.

Randomisation and masking :

An interactive web-response system (IWRS) was used to randomly assign participants to open-label onceweekly icodec or once-daily glargine U100, **both** in combination with 2 to 4 daily injections of aspart.

Participants were centrally randomly assigned to the next available treatment according to the randomisation schedule.


746 individuals screened
164 excluded or withdrew
146 screening failures
18 withdrew before randomisation
582 randomly assigned
291 randomly assigned to insulin icodec
291 randomly assigned to insulin glargine U100
17 permanent discontinuation of treatment
6 withdrawal of consent
4 adverse events
3 lost to follow-up
4 other*
22 permanent discontinuation of treatment
8 withdrawal of consent
3 adverse events
6 lost to follow-up
5 other†
274 (94%) completed week 26 visit without permanent discontinuation
269 (92%) completed week 26 visit without permanent discontinuation

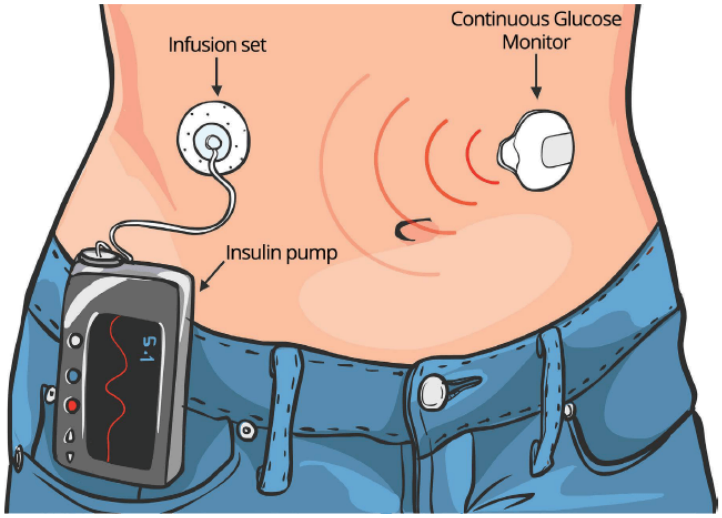
Procedures of the trial :

	Icodec (700U/ml)	Glargine (10U/ml)	Aspartat (100U/ml)
Hour :	Administered subcutaneously once weekly. on the same day of the week at any time of the day.	administered subcutaneously once daily, at the same time each day.	administered subcutaneously with main meals two to four times a day.
Dose :	The weekly icodec dose was calculated by multiplying the pre-trial daily basal insulin dose by seven. *** For the first injection only, a one-time additional 50% icodec dose was administered. From week 2, participants received the calculated once-weekly dose, with further increments based on weekly titrations guided in subsequent weeks, as needed, to attain a pre-breakfast glucose value of 80–130 mg/dL (4·4–7·2 mmol/L).	switched unit-to-unit from pretrial basal insulin in accordance with the local label.	Switched unit-to-unit from pretrial bolus insulin (per meal). For both randomly assigned groups.
	After randomisation, weekly titration of both icodec and glargine U100 were based on three pre-breakfast selfmeasured blood glucose (SMBG) values measured 2 days before titration and on the injection day		

- Throughout the treatment period, participants continued with any pre-trial, non-insulin glucose-lowering medications at their stable, pre-trial dose and frequency except for “sulphonylureas” and “glinides”,which were discontinued at randomisation to minimise the risk of hypoglycaemia.

- Participants were instructed to measure pre-prandial and bedtime values and record them in their electronic diary until the end of the trial.

(A blood glucose meter and electronic diary were provided to participants.)



- A continuous glucosemonitoring (CGM) (estimates the glucose level is every few minutes and keeps track of it over time)

device was worn intermittently during the trial and during the follow up period.

The CGM readings were blinded to both the participant and the investigator and were not used to inform any insulin dose titrations.

Outcomes :

The primary outcome was:

- The change in HbA1c from baseline to week 26.

Secondary efficacy outcomes included:

- The change in fasting plasma glucose (FPG) from baseline to week 26.
- Percentage of time in the target glycaemic range(70–180 mg/dL [3·9–10·0 mmol/L]), from week 22 to week 26.

Safety outcomes included :

- The mean weekly total insulin dose from week 24 to week 26.
- Change in bodyweight from baseline to week 26.
- the number of overall clinically significant hypoglycaemic episodes severe and non severe.

The primary hypothesis to be tested was that icodec was non-inferior to glargine U100 in terms of change in HbA1c from baseline to week 26.

Participants' baseline demographics + insulin type + dose at screening and concomitant glucose-lowering medications at screening were similar across both treatment groups

	Insulin icodec (n=291)	Insulin glargine U100 (n=291)
Male	154 (53%)	150 (52%)
Female	137 (47%)	141 (48%)
Age, years	59·7 (10·1)	59·9 (9·9)
Bodyweight, kg	85·5 (17·6)	83·1 (17·3)
BMI, kg/m²	30·5 (5·0)	30·0 (5·0)
Diabetes duration, years	18·0 (9·1)	16·3 (7·7)
HbA_{1c}, %	8·29 (0·86)	8·31 (0·90)
HbA_{1c}, mmol/mol	67·11 (9·41)	67·35 (9·79)
Fasting plasma glucose, mmol/L	9·2 (3·0)	9·6 (3·5)
Fasting plasma glucose, mg/dL	167 (54)	173 (63)

- Mean age at baseline was 59 ·8 years.
- Mean HbA1c concentration at baseline was 8 ·30% .
- Mean BMI at baseline was 30 ·3 kg/m²

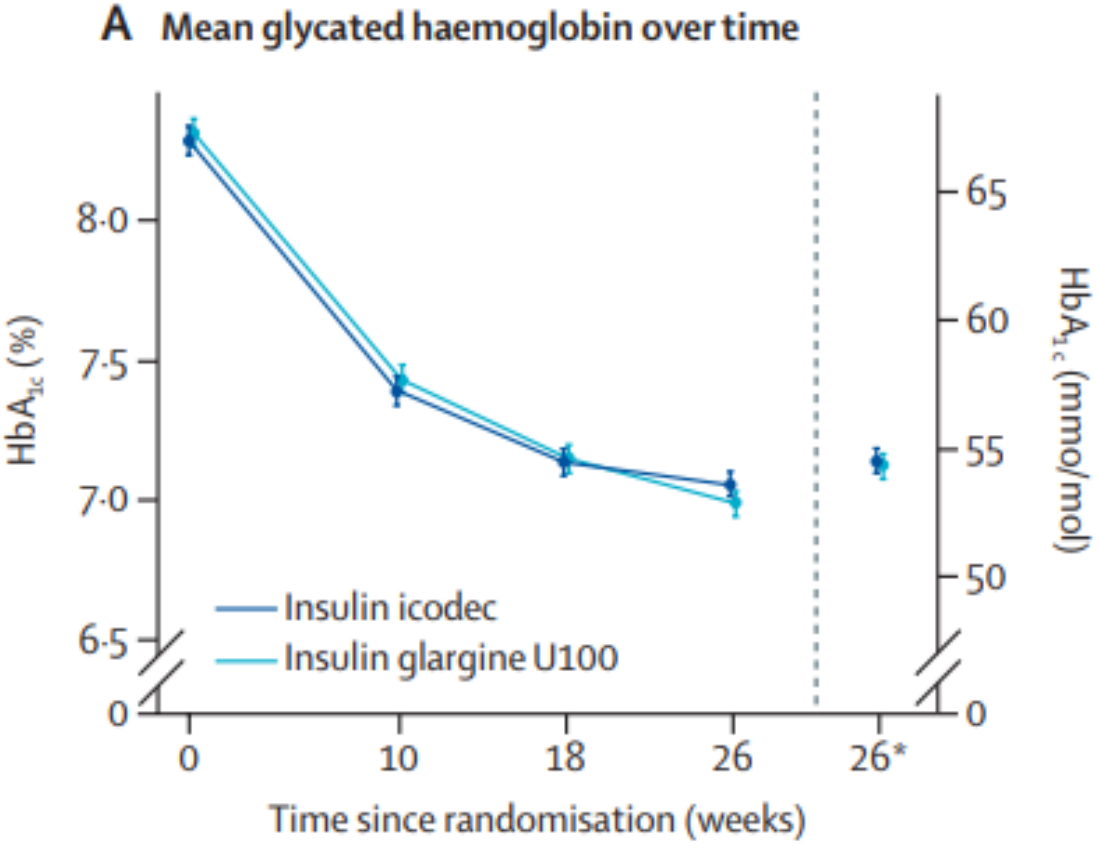
The mean HbA1c

In the icodec group :

decreased from 8 ·29% (SD 0 ·86) at baseline to an estimated mean of 7 ·14% (SE 0 ·05) at week 26 (1 ·16 percentage points)

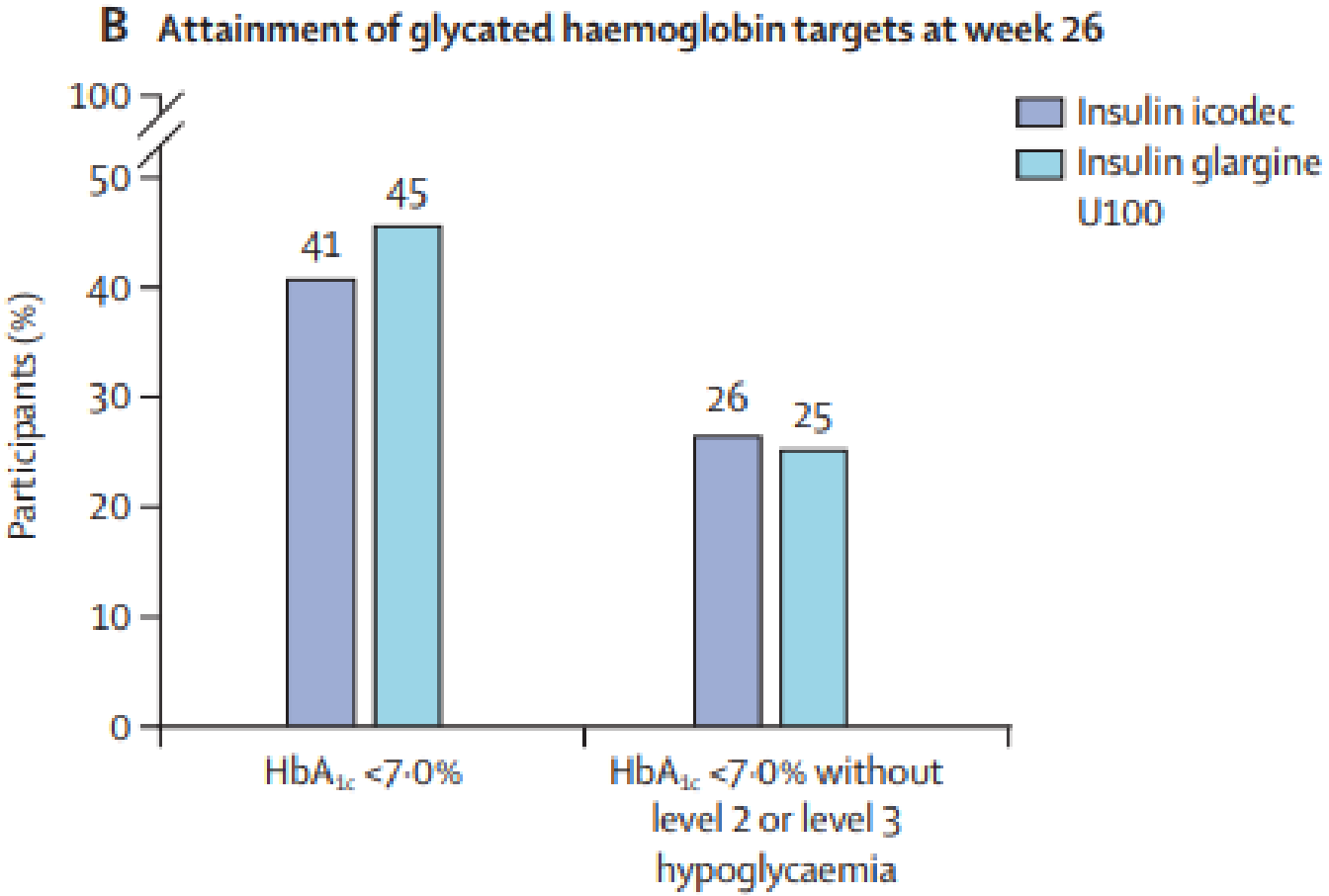
In the glargine U100 group:

decreased from 8 ·31% (SD 0 ·90%) to 7 ·12% (1 ·18 percentage points)



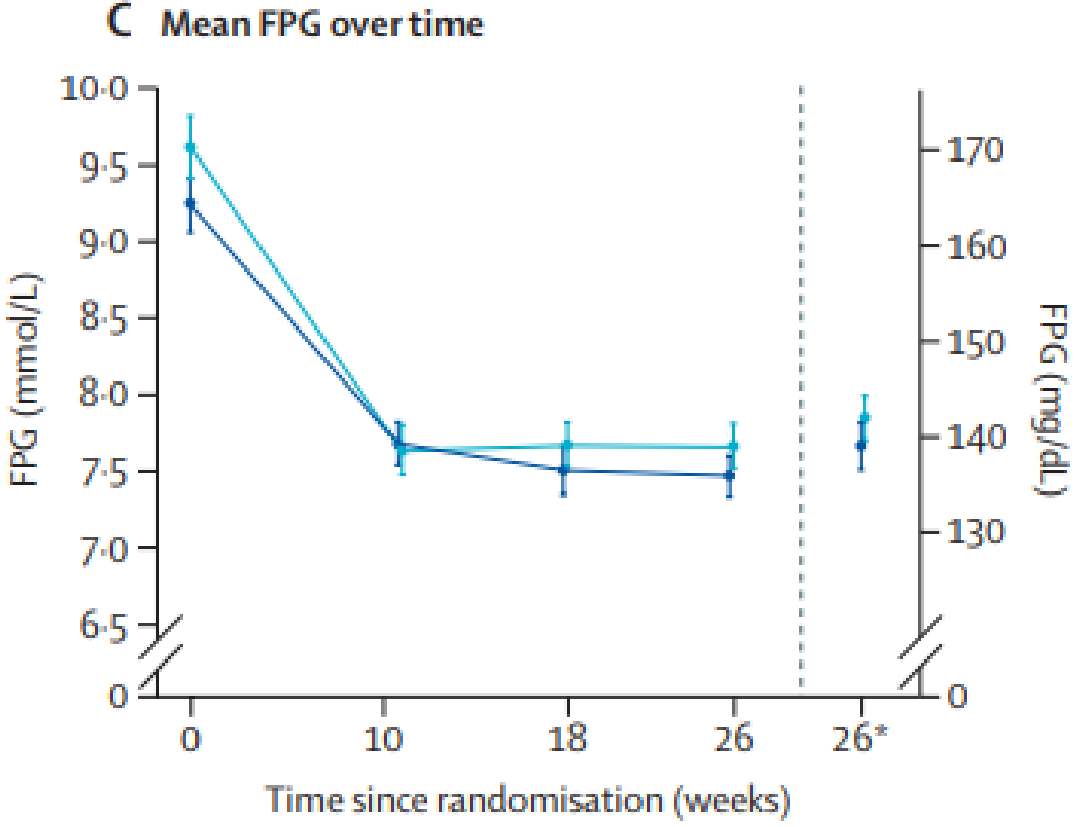
which shows the non-inferiority of icodec ($p<0.0001$) compared to glargine U100.

The odds of participants having an HbA1c below 7% at week 26 did not differ between treatments
(41% in icodec group vs 45% inglargine U100 group)



FPG concentrations decreased from baseline to week 26 in both groups and the estimated change from baseline to week 26 in FPG concentration was :

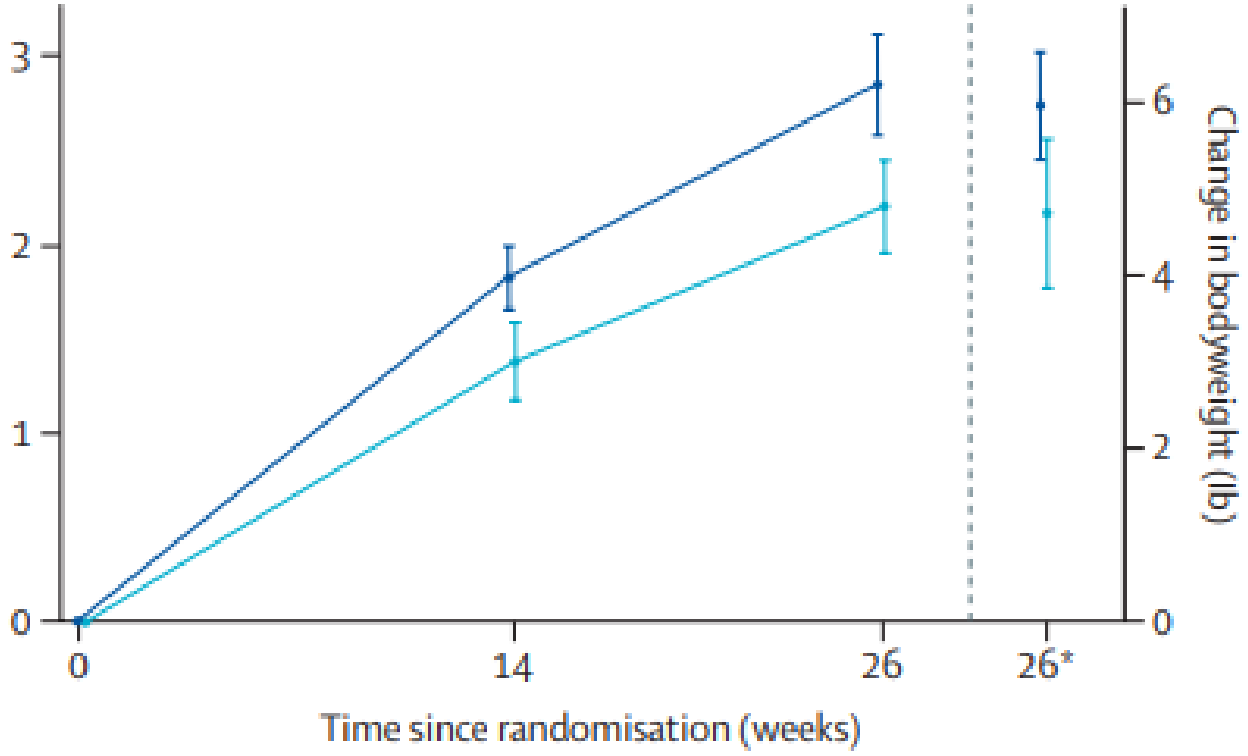
- 32 mg/dL (−1 ·75 mmol/L) in the **icodec group**
- 29 mg/dL in th **glargine group**



the result was not statistically significant

From baseline, mean increases in bodyweight did not differ between treatment group (2·7 kg [SE 0·3] in the icodec group vs 2·2 kg [0·4] in the glargine U100 group; ETD 0·57 kg [95% CI −0·39 to 1·54], p=0·24; figure 3D).

D Change from baseline to week 26 in bodyweight



The rates of level 1 hypoglycaemia were significantly higher in the icodec group than the glargine U100 group
icodec group had level 2 or level 3 hypoglycaemia, as did as participants in the glargine U100 group.

	Insulin icodec (n=291)		Insulin glargine U100 (n=291)		Insulin icodec *vs* insulin glargine U100
	Participants (%)	Episodes (rate per PYE)	Participants (%)	Episodes (rate per PYE)	ERR (95% CI), p value
Hypoglycaemic episodes (overall)					
Hypoglycaemia alert value (level 1)*	244 (84%)	5264 (31·45)	251 (86%)	4145 (24·85)	1·25 (1·03–1·52), p=0·025
Clinically significant (level 2) hypoglycaemia†	148 (51%)	937 (5·60)	160 (55%)	935 (5·61)	0·99 (0·73–1·34), p=0·93
Severe (level 3) hypoglycaemia‡	4 (1%)	7 (0·04)	2 (1%)	3 (0·02)	2·19 (0·20–24·44), p=0·53
Combined clinically significant (level 2)† or severe (level 3)‡ hypoglycaemia	150 (51%)	944 (5·64)	162 (56%)	938 (5·62)	0·99 (0·73–1·33), p=0·93

Conclusion :

- This trial showed that once-weekly icodec was non-inferior to once-daily glargine U100 with respect to the primary outcome, which was change in HbA1c from baseline to week 26.

- Rates of level 1 hypoglycaemia, which serves as an alert value, were significantly higher in the icodec group than in the glargine U100 group.

•The observed rates of overall or nocturnal combined clinically significant level 2 or level 3 hypoglycaemia were similar between icodec and glargine U100 groups. As would be expected in this population with long-standing on a basal-bolus regimen.