Once-weekly insulins: ONWARDS and upwards?

In this study by Philis-Tsimikas and colleagues, switching to once-weekly insulin icodec versus daily insulin degludec in adults with type 2 diabetes poorly controlled on once- or twice-daily basal insulin resulted in significant HbA_{1c} reduction. ONWARDS 2 was an open-label, treat-to-target, phase 3 randomised controlled trial conducted in 526 people with type 2 diabetes and a mean HbA_{1c} of around 65 mmol/mol at baseline. At 26 weeks, participants achieved mean HbA_{1c} values of 55.2 mmol/mol with icodec, versus 57.6 mmol/mol with degludec (estimated treatment difference –2.4 mmol/mol; *P*=0.003 for superiority). Hypoglycaemic events, particularly level 1, were significantly increased in icodec recipients versus those on degludec, but overall rates were low, with less than one level 2 (clinically significant) or level 3 (severe) hypoglycaemic event per person-year of exposure in both groups. Combined level 2 and 3 hypoglycaemia events were numerically but not significantly increased in those treated with icodec versus degludec. More people achieved HbA_{1c} levels of <53 mmol/mol and ≤48 mmol/mol, without level 2 or 3 hypoglycaemia, when treated with icodec than with degludec. However, those switching to icodec gained a mean of 1.40 kg over 26 weeks, while those switching to degludec lost a mean of 0.30 kg. At present, there are no weekly basal insulins, including icodec, licensed for use in the UK.

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It has been suggested that once-weekly insulin could improve acceptability and adherence compared with daily or twice-daily injections (Peyrot et al, 2012), and this is supported by studies of once-weekly versus daily GLP-1 receptor agonist treatments (Weeda et al, 2021). In the present phase 3, open-label randomised controlled trial, ONWARDS 2, the authors sought to explore the efficacy and safety of insulin icodec, an ultra-long-acting basal insulin analogue with a half-life of 196 hours. The half-life is due to lower affinity for the insulin receptor and strong, reversible binding to albumin, which provides a depot from which the insulin is slowly released, providing near-even glucose lowering and allowing once-weekly subcutaneous dosing.

A total of 526 people with type 2 diabetes poorly controlled on once- or twice-daily insulin regimens were randomised to switch to appropriate doses of once-weekly icodec or daily degludec (including an initial, additional 50% dose of icodec). Doses were then titrated weekly in both groups, aiming for fasting glucose of 4.4–7.2 mmol/L. Stable doses of oral glucose-lowering drugs were continued during the study, except for sulfonylureas and glinides, which were stopped at randomisation. People with an HbA_{1c} of 53–86 mmol/mol were included, and the mean HbA_{1c} values at baseline were around 65 mmol/mol in the two groups. Participants were followed for 26 weeks.

The primary outcome was change in HbA_{1c} from baseline to 26 weeks. Secondary and additional prespecified outcomes included:

- Clinically significant hypoglycaemia (level 2: <3 mmol/L), severe hypoglycaemia (level 3: cognitive impairment and third-party intervention needed) and a combination of the two.
- Changes in body weight.
- Time in Range (3.9–10.0 mmol/L), time below 3 mmol/L and time above 10 mmol/L were assessed via CGM during weeks 22–26 (CGM readings were not available to patients or clinicians to titrate insulin or to identify hypoglycaemia).

Citation: Brown P (2023) Diabetes Distilled: Once-weekly insulins – ONWARDS and upwards? *Diabetes & Primary Care* **25**: [early view publication]

Further reading

Insulin resources from *Diabetes & Primary Care*:

How to minimise insulin errors

The steps that should be taken to reduce the risks involved in the prescribing, preparation and administration of insulin.

Diabetes & Primary Care **24**: 181–2

Click here to access

How to calculate the amount of insulin to prescribe per month

Reducing waste whilst ensuring patients have enough to last.

Diabetes & Primary Care **24**: 183–4

Click here to access

How to support best practice injection technique

Essential information to ensure a user's insulin therapy is safe and effective.

Diabetes & Primary Care **24**: 185–6

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- Numbers achieving HbA_{1c} <53 mmol/mol or ≤48 mmol/mol, with and without level 2 or 3 hypoglycaemia.
- All adverse events were documented and collated.

Results

Although the study was designed to confirm whether weekly icodec treatment would be non-inferior to daily degludec in achieving the primary outcome, at 26 weeks, those treated with icodec achieved both non-inferior and statistically superior reductions in HbA_{1c}; mean HbA_{1c} fell from 65.8 to 55.2 mmol/mol on icodec, versus a reduction from 65.0 to 57.6 mmol/mol in those treated with degludec (estimated treatment difference –2.4 mmol/mol; $P<0.001$ for non-inferiority and $P=0.003$ for superiority). Mean body weight increased by 1.4 kg in the icodec group versus a reduction of 0.30 kg in the degludec group.

Level 1 hypoglycaemic events (measured glucose <3.9 mmol/L) were significantly more common in those treated with icodec than degludec (7.79 versus 3.86 events per person-year of exposure). Combined level 2 and 3 hypoglycaemic event rates were low (and lower than in previous trials of degludec and glargine), and were identified in 14% versus 7% of icodec and degludec recipients, respectively (a non-significant difference). There were no severe hypoglycaemic events in those treated with icodec and only one in those treated with degludec. Overall, 61% of those receiving icodec and 50% of those receiving degludec experienced an adverse event, with 8% and 6% suffering a serious adverse event, respectively; however, rates of withdrawal from the study were low.

No new safety issues were identified with icodec. However, any increased level of hypoglycaemia may be important, especially when considering elderly people and those with decreased hypoglycaemia awareness.

There were no significant differences between groups in terms of CGM measurements, with both groups achieving around 60% Time in Range and similar proportions of time above and below range.

Sulfonylureas were stopped at randomisation (used by just under a quarter of participants), yet in clinical practice they are commonly continued with a 50% dose reduction when insulin is initiated, so it will be important in future studies, such as ONWARDS 3 and 5, to clarify the potential impact of combination sulfonylurea and icodec treatment on hypoglycaemia.

After 100 years of insulin use, and many failed attempts to improve insulin acceptability and to improve clinical inertia around insulin initiation, ongoing studies with once-weekly basal insulins (both icodec and others in development) suggest these may finally reach the market and represent a significant advance (Rosenstock and Del Prato, 2022). However, as the authors of an accompanying comment in *Lancet Diabetes & Endocrinology* discuss, whether once-weekly dosing will prove to be safe and translate into greater adherence and efficacy still requires further study (Bellary and Barnett, 2023).

Readers seeking to learn more about weekly insulins are directed to an open access review by Rosenstock and Del Prato (2022).

Basal insulin icodec and other once-weekly basal insulins are not yet licensed in the UK or Europe. ■

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

Click here to read the study in full

Bellary S, Barnett AH (2023) Insulin icodec: Evolution or revolution in diabetes therapy? *Lancet Diabetes Endocrinol* 4 May [Epub ahead of print]. https://doi.org/10.1016/S2213-8587(23)00125-0

Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM (2012) Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabet Med* **29**: 682–9

Rosenstock J, Del Prato S (2022) Basal weekly insulins: The way of the future! *Metabolism* **126**: 154924

Weeda ER, Muraoka AK, Brock MD, Cannon JM (2021) Medication adherence to injectable glucagon-like peptide-1 (GLP-1) receptor agonists dosed once weekly vs once daily in patients with type 2 diabetes: A meta-analysis. *Int J Clin Pract* **75**: e14060