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Short communication

DOI: https://doi.org/10.3329/jacedb.v5i2.90516

Journal of Association of Clinical Endocrinologist and Diabetologist of Bangladesh
July 2026, Vol. 5, No. 2, e90516

ISSN (Online): 2959-8176
ISSN (Print): 2958-0307

Once-weekly basal insulin: A measured advance

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Abstract

Insulin icodec, the first once-weekly basal insulin analogue, addresses a longstanding barrier to insulin initiation: the burden of daily injections. By binding reversibly to albumin via a C20 fatty diacid chain, icodec achieves a half-life of approximately 196 hours, enabling stable glucose lowering throughout the week from a single subcutaneous dose. Across the ONWARDS phase 3 program, icodec demonstrated at least noninferior, and in several trials statistically superior, glycated hemoglobin (HbA1c) reduction compared with once-daily basal insulin analogues in type 2 diabetes. The hypoglycemia signal was variable across type 2 diabetes trials but consistently and significantly elevated in type 1 diabetes. The prolonged pharmacokinetic profile confers an important limitation: dosing errors carry sustained consequences, and the effects of an administered dose cannot be rapidly reversed. For patients in whom injection burden is the primary barrier to insulin initiation, a once-weekly option may resolve years of clinical inertia. Nevertheless, this is a measured advance. Clinicians must weigh the convenience of weekly dosing against pharmacokinetic inflexibility, a modest but present hypoglycemia signal, and access barriers that may exclude the patients who stand to benefit most. *[J Assoc Clin Endocrinol Diabetol Bangladesh,* July 2026; 5 (2): e90516*]*

Keywords: Insulin icodec, basal insulin, type 2 diabetes, ONWARDS, once-weekly insulin

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Consider a 58-year-old woman with long-standing type 2 diabetes whose HbA1c remains above 9%, accompanied by unintentional weight loss, despite the need for treatment intensification. Although basal insulin is indicated, she declines to initiate it because of the burden of daily injections; a pattern that is common and costly. In current practice, after metformin, either a glucagon-like peptide-1 receptor agonist or basal insulin is a preferred second-line agent; basal insulin is always effective and is especially important when glycemic targets remain unmet or catabolic features are present.[1] Insulin icodec, the first once-weekly basal insulin analogue, was developed for patients like her: those who stand to benefit from basal insulin but are held back not by a lack of indication, but by the daily reminder of chronic illness that each injection carries.

Insulin icodec is a modified insulin with three amino acid substitutions and a C20 fatty diacid chain that binds reversibly to albumin, creating a circulating depot.[2] The half-life is approximately 196 hours, and steady state is reached after three to four weekly injections.[2] The glucose-lowering effect of insulin icodec is relatively stable throughout the week; however, its prolonged duration of action means that the effects of an administered dose cannot be rapidly reversed. Consequently, dosing errors, such as an accidental additional dose, may result in sustained insulin exposure and an increased risk of hypoglycemia. To minimize the risk of accidental overdosing, insulin icodec should be administered only using its dedicated prefilled pen, and patients should be carefully instructed on correct dose selection and injection technique. Education of patients, caregivers, and pharmacies is essential, particularly during treatment initiation and transitions from other insulin regimens.[2]

The ONWARDS phase 3 program tested whether a weekly injection could match daily basal insulin in glycemic control. In insulin-naïve patients, insulin icodec achieved a statistically superior reduction in HbA1c compared with once-daily insulin glargine U100

in ONWARDS 1, with a between-group difference of −0.19 percentage points (95% CI, −0.36 to −0.03) at 52 weeks.[3] In ONWARDS 3, once-weekly insulin icodec demonstrated a statistically significant greater reduction in HbA1c compared with once-daily insulin degludec, with an estimated treatment difference of approximately −0.2 percentage points (95% CI, −0.3 to −0.1) at 26 weeks.[4] When coupled with a dosing guide app in ONWARDS 5, once-weekly insulin icodec reduced HbA1c by an estimated treatment difference of –0.38 percentage points (95% CI, –0.66 to –0.09) compared with once-daily basal insulin analogs, confirming noninferiority (P<0.001) and superiority (P=0.009).[5] In patients already on basal insulin, switching to icodec demonstrated noninferiority and statistical superiority in HbA1c reduction versus degludec in ONWARDS 2 (estimated treatment difference, −0.22 percentage points; 95% CI, −0.37 to −0.08; p=0.0028), although the absolute difference was modest.[6] In type 1 diabetes, ONWARDS 6 showed that once-weekly icodec was noninferior to once-daily degludec in HbA1c reduction, with an estimated treatment difference of 0.05 percentage points (95% CI, −0.13 to 0.23) at 26 weeks, confirming noninferiority (P=0.0065).[7] All ONWARDS trials were open-label, treat-to-target studies, but the consistency of glycemic outcomes across these comparisons, ranging from at least noninferior to, in several cases, statistically superior, confirms that once-weekly dosing does not come at the expense of glucose control. The advantage of insulin icodec, therefore, lies not in a marginally greater HbA1c reduction but in the radical simplification of the regimen.

More concerning is the hypoglycemia signal. In ONWARDS 1 (insulin-naïve adults with type 2 diabetes), clinically significant hypoglycemia occurred at a numerically higher rate with icodec than with glargine; the difference was not significant at 52 weeks (rate ratio, 1.64; 95% CI, 0.98 to 2.75) but reached significance by week 83 (rate ratio, 1.63; 95% CI, 1.02 to 2.61).[3] In ONWARDS 2 (adults with type 2 diabetes on basal insulin), the rate of clinically significant hypoglycemia was numerically higher with icodec than with degludec, but the difference was not statistically significant (0.73 vs. 0.27 events per patient-year; rate ratio, 1.93; 95% CI, 0.93 to 4.02).[6] In ONWARDS 3 (adults with insulin-naïve type 2 diabetes), level 2 or 3 hypoglycemia was more frequent with icodec than degludec (statistically significant at 26 weeks, but not over the full 31-week follow-up).[4] In ONWARDS 5 (insulin naïve type 2 diabetes; icodec dose guided by an app vs. investigator titrated once daily basal insulin), clinically significant hypoglycemia was low and similar between once-weekly icodec and daily basal insulin analogues.[5] In ONWARDS 6 (type 1 diabetes), clinically significant hypoglycemia was significantly higher with icodec than with degludec at week 26 (19.9 vs. 10.4 events per patient-year; rate ratio 1.9 [95% CI 1.5 to 2.3]; P<0.0001).[7] Taken together, the ONWARDS trials show a hypoglycemia signal that is modest in type 2 diabetes, reaching statistical significance in ONWARDS 1 (by week 83) and ONWARDS 3 (at week 26), though not in ONWARDS 2 or 5, whereas it is substantially larger and consistently significant in type 1 diabetes. These findings suggest that the risk of hypoglycemia with insulin icodec may be population-dependent and should be interpreted in the context of individual patient characteristics **(Table-I)**.

Nocturnal hypoglycemia, which is of particular concern because it may pass unrecognized during sleep, showed the same population dependence. In the insulin-naïve type 2 diabetes setting, the available trial-specific data are reassuring: in ONWARDS 3, only 2 nocturnal level 2 or 3 episodes occurred with icodec compared with 5 with degludec over the 31-week period.[4] In ONWARDS 5, rates of nocturnal clinically significant hypoglycemia were low and similar between groups, with 0.02 events per patient-year of exposure for icodec and 0.03 events per patient-year for once-daily basal insulin analogues.[5] In type 1 diabetes, by contrast, the excess hypoglycemia observed with icodec extended into the nocturnal period, with nocturnal clinically significant or severe hypoglycemia significantly more frequent with icodec than with degludec in ONWARDS 6 (P<0.0001 at weeks 26 and 57).[7] Because the glucose-lowering effect of a weekly dose cannot be rapidly down-titrated, this nighttime signal in type 1 diabetes reinforces the need for careful patient selection, conservative titration, and structured education when a once-weekly basal insulin is considered.[2]

For appropriate candidates, the practical regimen is straightforward. Insulin icodec is administered once weekly as a subcutaneous injection on the same day each week, at any time of day. In insulin-naïve individuals, the recommended starting dose is 70 units once weekly. When switching from once-daily basal insulin, the first dose of insulin icodec should be administered on the day after the last dose of the

Table-I: Efficacy and hypoglycemia outcomes across the ONWARDS trials

Trial	Population; comparator vs once-weekly icodec	HbA1c efficacy	Clinically significant or severe hypoglycemia	Nocturnal hypoglycemia
ONWARDS 1	Insulin-naïve T2D; once-daily glargine U100	Superior reduction; ETD −0.19 pp (95% CI, −0.36 to −0.03) at 52 wk; noninferiority confirmed, superiority P=0.02	Numerically higher with icodec; not significant at 52 wk (0.30 vs 0.16 events/PYE; RR 1.64, 95% CI 0.98 to 2.75); significant by wk 83 (RR 1.63, 95% CI 1.02 to 2.61)	—†
ONWARDS 2	Basal insulin–treated T2D; once-daily degludec	Noninferior and superior; ETD −0.22 pp (95% CI, −0.37 to −0.08); NI P<0.0001, superiority P=0.0028	Numerically higher with icodec, but not significantly different (0.73 vs 0.27 events/PYE; RR 1.93, 95% CI 0.93 to 4.02)	—†
ONWARDS 3	Insulin-naïve T2D; once-daily degludec	Superior reduction; ETD −0.2 pp (95% CI, −0.3 to −0.1) at 26 wk; NI P<0.001, superiority P=0.002	Level 2 or 3 more frequent with icodec; significant at wk 26 (0.35 vs 0.12 events/PYE; P=0.01) but not over 31 wk (0.31 vs 0.15; P=0.11)	Fewer with icodec: 2 (icodec) vs 5 (degludec) level 2 or 3 episodes over 31 wk
ONWARDS 5	Insulin naïve T2D; once daily basal insulin analogues (degludec, glargine U100, or glargine U300)	Superior reduction; ETD −0.38 pp (95% CI, −0.66 to −0.09); NI P<0.001, superiority P=0.009	Icodec (with app) vs OD analogues: 0.19 vs. 0.14 events/PYE; rate ratio 1.17 (95% CI 0.73–1.86), not significant.	Nocturnal clinically significant hypoglycemia: Icodec 0.02 vs OD 0.03 events/PYE; numerically very small difference.
ONWARDS 6	T1D on basal–bolus regimen; once-daily degludec	Noninferior to degludec; ETD 0.05 pp (95% CI −0.13 to 0.23) at 26 wk; noninferiority P=0.0065	Significantly higher with icodec at wk 26 (19.9 vs 10.4 events/PYE; RR 1.9, 95% CI 1.5 to 2.3; P<0.0001); over 57 weeks (17.0 vs 9.16 events/PYE, RR 1·80, 95% CI 1·48 to 2·18; p<0·0001)	Significantly higher with icodec (P<0.0001 at wk 26 and 57)

Data are from the primary ONWARDS trial publications. HbA1c treatment differences (icodec minus comparator) are expressed in percentage points (pp); negative values favor icodec.
† Not extracted; full text not accessible.
Abbreviations: CI, confidence interval; ETD, estimated treatment difference; NI, noninferiority; pp, percentage points; PYE, patient-year of exposure; RR, rate ratio; T1D, type 1 diabetes; T2D, type 2 diabetes; wk, week(s); OD, once daily basal insulin analogue.

previous basal insulin. The Week 1 dose is calculated as 1.5 times the total daily basal insulin dose multiplied by seven, rounded to the nearest 10 units, followed in Week 2 by a dose equivalent to the weekly basal insulin requirement (total daily dose multiplied by seven, rounded to the nearest 10 units). From Week 3 onwards, dosing is titrated based on individual metabolic requirements, self-monitored blood glucose profiles, and

predefined glycemic targets.[8]

Reducing the number of injections from 365 to 52 per year is a meaningful reduction in treatment burden. For patients who delay or decline basal insulin because of injection fatigue, stigma, or the daily reminder of illness, a once-weekly option may help overcome clinical inertia. Convenience alone, however, is not a clinical endpoint. If weekly dosing creates a false sense that diabetes is milder or leads to reduced attention to other aspects of self-care, the net effect could be negative. In many settings, cost will also be a decisive barrier. Without tiered pricing or inclusion in essential medicines frameworks, patients who stand to benefit most, particularly those in low- and middle-income countries where access to daily basal insulin is already inconsistent, may be unable to access the therapy.

The index patient also illustrates that the choice between basal insulin and a GLP-1 receptor agonist at a given HbA1c is phenotype dependent rather than automatic. When features of ongoing catabolism predominate, such as unintentional weight loss, ketosis, or symptomatic and markedly elevated glucose levels, insulin is the appropriate, and sometimes urgent, choice. In these situations, a GLP-1 receptor agonist alone may be insufficient. Conversely, in a person with obesity and established atherosclerotic cardiovascular disease, or who is at high cardiovascular risk, a GLP-1 receptor agonist with proven cardiovascular and weight benefits may be preferred at the same HbA1c of 9%. The woman described here was deliberately presented as someone in whom basal insulin is clearly indicated and for whom injection burden is the sole barrier. It is precisely this phenotype, rather than the broader population of injectable-eligible patients, for whom a once-weekly basal insulin is most compelling.[1]

The most profound change may be in the clinical conversation. “We can consider insulin, and a weekly option exists,” is a sentence that may cut through years of reluctance for some patients. However, this represents a measured advance, not a panacea. Clinicians must individualize treatment decisions, weighing the convenience of a weekly regimen against a small but consistent increase in hypoglycemia risk, pharmacokinetic inflexibility, and the established role of basal insulin, now available as a weekly injection, which remains a cornerstone of therapy for many patients.

Acknowledgements

None.

Funding/Support

No funding was received for this work.

Conflict of interest

The author declares no conflicts of interest.

Declaration of Generative AI Use

During the preparation of this work, the author used Claude (Anthropic) to assist with drafting and language editing of portions of the manuscript and with formatting of in-text citations and references. After using this tool, the author thoroughly reviewed, edited, and modified the content as needed and takes full responsibility for the accuracy, originality, and integrity of the final work.

Ethical Approval

Ethical approval was not required for this article because no human participants, patient data, or identifiable information were involved.

Data availability statement

No new data were generated or analyzed in support of this article.

Author contributions

The author (SMM) contributed to the conception, drafting, critical revision, and final approval of the manuscript.

How to cite this article: Sarker MM. Once-weekly basal insulin: A measured advance. J Assoc Clin Endocrinol Diabetol Bangladesh 2026; 5(2): e90516. DOI: https://doi.org/10.3329/jacedb.v5i2.90516

Publication History

Received on: 05 Jun 2026

Accepted on: 29 Jun 2026

Published on: 01 Jul 2026

Responsible editor

Mashfiqul Hasan (ORCID ID https://orcid.org/0000-0002-1805-5187)

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