Scientific Research Publishing

Open Journal of Internal Medicine, 2025, 15(2), 97-106
https://www.scirp.org/journal/ojim
ISSN Online: 2162-5980
ISSN Print: 2162-5972

Once Weekly Insulin: The Battle of 52 versus 365

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How to cite this paper: Thomas, J.J. and Mathews, N. (2025) Once Weekly Insulin: The Battle of 52 versus 365. *Open Journal of Internal Medicine*, **15**, 97-106.
https://doi.org/10.4236/ojim.2025.152010

Received: April 23, 2025
Accepted: May 19, 2025
Published: May 22, 2025

Abstract

The ever-growing global diabetes burden is an uphill battle for drug manufacturers. Insulin serves as the go-to drug in the treatment of diabetes when all others fail. The development of this drug has matured with time into more purified human formulations from the older bovine and porcine preparations, as well as the newer available analogues, which give greater flexibility from ultra-short acting to long-acting basal formulations. Short or rapid-acting insulins predominantly focus on the prandial sugar spikes, while the longer-acting and basal insulins work on the fasting glucose levels. Prandial or short-acting insulins are administered with the number of meals taken; while the basal insulin is taken once daily, usually at bedtime and works for ≥24 hours. However, this still warrants the basal insulin to be taken every 24 hours. In this article, we focus on a newer formulation of insulin that is proposed to act for a week, thereby reducing the number of injection jabs considerably and contributing towards increased patient compliance. This would translate to better HbA1c reduction and curb the onset of both micro- and macro-vascular complications seen in diabetes.

Keywords

Type 2 Diabetes Mellitus, Insulin, Once Weekly Dose, Basal Insulin, HbA1c

1. Global Diabetes Burden

According to the International Diabetes Federation (IDF) report of 2021, 10.5% of the adults aged between 20 - 79 years are affected by diabetes. Among those affected, 50% of them are unaware that they have this ailment. This total number is further projected to grow to 46% by 2045, *i.e.*, 1 in every 8 adults would be affected by diabetes. [1] Prevalence data from 200 countries between the years 1990 and

2022 showed that it increased from 7% - 14% between 1990 and 2022, respectively. This translates to an alarming increase of 630 million adults added to the diabetes pool from 1990 to 2022, seen mainly in low- and middle-income countries. [2] In developed countries like the U. S., the number of diagnosed diabetics is projected to increase by 165%, from 11 million in 2000 to 29 million in 2050. Persons aged over 75 years and African-Americans will have the highest increase, 336% and 275% respectively. An additional 18 million people will be diagnosed with diabetes in the U. S. alone. 37% of this can be attributed to changes in age, population, sex and race and 27% due to population growth, 36% due to changes in the prevalence rates. [3] This growing population of individuals with diabetes warrants a more effective regimen in hyperglycemia treatment to circumvent potential complications arising due to poor glycemic control. Oral hypoglycemic agents (OHAs), injectable non-insulin formulations and injectable insulins, in the present day armamentarium, contribute towards controlling hyperglycemia reduction. However, patient adherence to multi-dose regimes increases the risk of poorer compliance and thus favors an increase in negative outcomes.

2. Insulin—History in the Making

In 1921, an orthopedic surgeon (Frederick Banting), a professor of physiology (John Macleod), a student research assistant (Charles Best), and a 3 member team led the initiation of a revolution in the treatment of diabetes, the proverbial "big bang" moment. Their research on 10 dogs from May to September 1921 demonstrated that a de-pancreatized dog developed hyperglycemia and that it was an intravenous injection of their pancreatic extract, initially called isletin, which decreased the high blood glucose. Following the purification techniques by biochemist J. B. Collip, the extract isletin was first injected in 1922 into a 14-year-old child, which caused a mild decrease in blood sugars. Further injections of the purified extract caused further decreases in blood glucose levels and glucosuria, along with the disappearance of ketonuria. [4]

The earlier insulin preparations were short acting, and it was the addition of protamine by a chemist H. C. Hagedorn and the inclusion of zinc by Scott and Fisher that led to the longer acting protamine zinc insulin, which lasted for 24 - 36 hours. Recombinant DNA technology paved the way for the first recombinant DNA (rDNA) human insulin by David Goeddel in 1978. Commercially available rDNA insulins like Humulin R (rapid) and Humulin N (NPH) appeared in 1982. Subsequent modifications in the amino acid chains in insulin altered the pharmacokinetics of the insulin, leading to faster absorption, an earlier peak of action and a shorter duration of action (Lispro, Aspart and Glulisine). While these addressed the prandial surges in glucose, longer-acting preparations that mimicked the basal physiological insulin secretion in the body were lacking. Basal insulins like Glargine and Detemir, approved in 2000 and 2005, respectively, prolonged the duration of action by forming micro precipitates at the injection site and slowing their absorption. The next generation of basal insulins, like insulin glargine U300 and in-

sulin degludec, demonstrated a duration of action of more than 24 hours and approximately 42 hours, respectively. These ultra-long-acting insulins also showed a lower risk of hypoglycemia when compared to prior long-acting insulins. [5]

3. The Weekly Dose

None of the oral hypoglycemic agents (OHAs) exhibited a prolonged half-life to warrant increased patient adherence and compliance with medications. Injectable insulins provided diabetic patients with the flexibility to use them once daily while on oral medications (either meal time or basal plus regimens) or titrate the number of doses depending on the number of meals, in addition to a bedtime basal dose of insulin.

The discovery of the entero-insular axis, wherein gut-derived chemical signaling exerts control over the endocrine pancreas, brought about a new class of medications in the fight against hyperglycemia. Oral preparations that worked on the dipeptidyl peptidase-4 (DPP4) enzyme and injectable incretin hormones, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) further strengthened the anti diabetes armamentarium. [6] Injectable medications working on the "incretin effect" were among the first anti diabetic medications to be administered in the once weekly dose (dulaglutide and semaglutide), the latest being a dual GIP/GLP-1 agonist (tirzepatide). The weight loss, along with the accompanying glucose reduction, has helped improve the overall micro- and macro-vascular complications seen in diabetes. [7]-[9]

Newer modes of drug delivery, which include using the respiratory pathway, have been under investigation for some time now. Although having earlier limited success, the newer Technosphere Insulin formulation, Afrezza, has been showing promising results in the control of prandial glucose control. [10] This still leaves the basal glucose control aspect of treatment unanswered. A single, weekly insulin dosing, in addition to this type of needle-free insulin delivery, would greatly benefit those persons with uncontrolled glucose levels, increase patient adherence and contribute towards better compliance.

4. Mechanism of Action

Some of the research involving prolonging the action of insulin and decreasing their peak to trough ratios involves linking them to polyethylene glycol (PEG) polymer chains or a fragment crystallizable (Fc) region of immunoglobulin G (IgG). Earlier studies using the PEGylation approach (AB101) and another similar elastin-like polypeptide (ELP)ylation approach (Insumera) were used to create two long-acting analogs, which have met with limited progress in their clinical development.

The process of linking the insulin to the Fc region of IgG confers on the molecule similar long half-lives to endogenous IgG. Three insulins developed using this process were basal insulin Fc (BIF), HM12460A and HM12470. Animal studies revealed that the half-life of HM12470 was 15 times longer than that of insulin

degludec, and its glucose-reducing effect was seen up to 7 days. [11] While all of the above were once weekly dosed, only BIF progressed to phase 2 clinical trials.

Another molecule, insulin icodec, incorporates insulin along with an attachment of a 20-carbon fatty diacid (icosanedioic acid) to the B chain of the insulin molecule, thus allowing a strong, reversible binding to albumin and a longer once weekly formulation.

5. Clinical Trials with Basal Insulin Fc (BIF)

BIF is an insulin and human immunoglobulin G2 (IgG2) fragment crystallizable (Fc) domain fusion protein that has selective and full agonism to insulin receptors.

A randomized, parallel, open-label study, conducted at 61 sites, in which 278 insulin-naive adult (18 - 75 years of age) patients with type 2 diabetes (T2D) were randomly assigned (1:1) to receive BIF once weekly or insulin degludec once daily over the 26-week treatment period. The primary end point was HbA1c change from baseline to week 26, and secondary end points included fasting blood glucose (FBG), six-point glucose profiles, and rates of hypoglycemia. Towards the end of the 26-week period, it was observed that BIF showed a noninferior HbA1c change from baseline versus degludec, with a treatment difference of 0.06% (90% CI −0.11, 0.24; P = 0.56). Both BIF and degludec achieved a mean HbA1c < 7% at week 26. Both of the treatment arms showed significant reductions in FBG from baseline, and no significant differences were seen in rates of hypoglycemia between the groups (BIF 0.22 events/patient/year, degludec 0.15 events/patient/year; P = 0.64) with an absence of severe hypoglycemia in both groups. Therefore, BIF showed a noninferior glycemic control compared with degludec as measured by HbA1c change from baseline to study endpoint, despite higher fasting glucose targets for BIF than for degludec. [12]

A randomized, open-label, comparator-controlled, 32-week study in adults (aged ≥ 18 years) with T2D who were previously treated with basal insulin and up to three oral antidiabetic medicines, performed in 44 sites, was done to check for the safety and efficacy of BIF. 399 subjects were randomized and divided into 3 groups: 2 in the BIF group (BIF-A1 and BIF-A2) and 1 in the degludec group. The FBG targets for BIF-A1, BIF-A2 and degludec groups were ≤7.8 mmol/L or ≤140 mg/dL; titrated every 2 weeks, ≤6.7 mmol/L or ≤120 mg/dL; titrated every 4 weeks, and ≤5.6 mmol/L or ≤100 mg/dL, respectively. The primary endpoint was the change in HbA1c from baseline to week 32. It was seen that BIF was non-inferior when compared to degludec in the change in HbA1c (0.1% [90% CI −0.1 to 0.3]). Additionally, the rates of hypoglycemia (≤3.9 mmol/L or ≤70 mg/dL) in the BIF groups were 25% lower than those observed in the degludec group (treatment ratio BIF-A1 versus degludec was 0.75 [0.61 - 0.93], and BIF-A2 versus degludec was 0.74 [0.58 - 0.94]). Thus, weekly BIF had a similar efficacy when compared to insulin degludec. [13]

A randomized, parallel, open-label, multicenter study conducted at 49 sites, in which 265 adult (18 - 75 years of age) patients with type 1 diabetes (T1D) previ-

ously treated with multiple daily basal injections, were randomly assigned (1:1) to receive BIF once weekly or insulin degludec once daily over the 26-week treatment period. The primary end point was HbA1c change from baseline to week 26 (non-inferiority margin, 0.4%) and secondary end points were percent time in range (TIR) (70 - 180 mg/dL) using continuous glucose monitoring (CGM), fasting glucose (FBG) level, and rates of observed hypoglycemia. Towards the end of the 26-week period, it was observed that BIF showed a noninferior HbA1c change from baseline versus degludec with a treatment difference of 0.17% (90% CI 0.01, 0.32; P = 0.07) favoring the comparator, *i.e.*, degludec. Despite the FBG values being significantly higher in the BIF group versus the degludec group (158.8 mg/dL versus 143.2 mg/dL, P = 0.003), the percentage TIR was similar in both (56.1% BIF versus 58.9% degludec, P = 0.112) groups and no significant differences in the rates of hypoglycemia between the two groups were seen. Therefore, once weekly BIF showed a noninferior glycemic control compared with once daily insulin degludec in T1D patients. [14]

6. Clinical Trials with Insulin Icodec

Insulin icodec is a basal insulin with an acylated analogue (icosanedioic acid) along with the replacement of 3 amino acids, which ensures a strong bond with albumin and a longer duration of action (estimated half-life of 196 h). [15]

A randomized, open-label, treat-to-target phase 3a trial, performed in 12 countries, involving 984 insulin naïve adults (≥18 years of age) with type 2 diabetes over 78 weeks (along with a 5-week follow-up period) was done to examine non-inferiority of insulin icodec to glargine U100 for efficacy and safety both in combination with noninsulin glucose-lowering treatments (including GLP-1 receptor agonists and sodium-glucose co-transporter 2 [SGLT2] inhibitors). The primary endpoint was HbA1c reduction at 52 weeks and secondary endpoints were percent time in range (TIR) (70 - 180 mg/dL) in weeks 48 to 52, change in the FBG from baseline to week 52 along with hypoglycemic episodes (from baseline to weeks 52 and 83) in each group. Subjects were randomly assigned in a 1:1 ratio to receive either a once-weekly insulin icodec or once-daily insulin glargine U100. It was seen that although FBG levels were similar in the two groups, the target glycemic range was better held in the icodec group than those receiving glargine U100 in weeks 48 to 52 (additional 1 hour and 1 minute per day) and weeks 74 to 78 (additional 1 hour and 4 minutes per day). The mean reduction in HbA1c at 52 weeks was greater with icodec than with glargine U100 (from 8.50% to 6.93% [mean change, −1.55 percentage points], from 8.44% to 7.12% [mean change, −1.35 percentage points], respectively). The combined clinically significant or severe hypoglycemia rates seen were 0.30 events per person-year of exposure with icodec and 0.16 events per person-year of exposure with glargine U100 at week 52 (estimated rate ratio, 1.64; 95% CI, 0.98 to 2.75). Therefore, once-weekly insulin icodec demonstrated better glycemic control than once-daily insulin glargine U100 in insulin naïve T2D adults. [16]

A randomized, open-label, active-controlled, multicentre, treat-to-target phase 3a trial, in 526 adults (≥18 years of age) patients with T2D, was done in 71 sites. Subjects recruited were randomly assigned (1:1) to receive either a once-weekly insulin icodec or once-daily insulin degludec for 26 weeks. The primary endpoint was change in HbA1c from baseline to week 26, and secondary endpoints were change in FBG, percent time in range (TIR) (70 - 180 mg/dL) using Continuous Glucose Monitoring (CGM) System, number of hypoglycemic events and change in body weight. Towards the end of the 26-week period, it was observed that HbA1c was reduced to a greater degree with insulin icodec than degludec (7.20% versus 7.42% [55.2 versus 57.6 mmol/mol], respectively), showing a non-inferiority ($p < 0.0001$) and superiority ($p = 0.0028$). Body weight increase was observed in the insulin icodec group (+1.4 kg) as compared to weight loss in the insulin degludec group (−0.3 kg). There were no significant differences between the two groups in terms of hypoglycemic or adverse events. Hence, the once-weekly icodec was non-inferior and superior to once-daily degludec as shown in HbA1c reduction after 26 weeks, albeit associated with a slight weight gain. [17]

A randomized, double-masked, noninferiority, treat-to-target, phase 3a trial was done in 11 countries among 588 adults (≥18 years of age) patients with T2D who were insulin naïve to assess the efficacy and safety of once-weekly icodec compared to once-daily insulin degludec. The primary end point was change in HbA1c from baseline to week 26, and secondary end points were change in FBG from baseline to week 26, mean weekly insulin dose during the last 2 weeks of treatment, body weight change from baseline to week 26, and number of hypoglycemic episodes in each group. Towards the end of the 26 week period, it was observed that the mean values of HbA1c level reduced from 8.6% to 7.0% and from 8.5% to 7.2% in the insulin icodec and insulin degludec groups, respectively (estimated treatment difference [ETD], −0.2 [95% CI, −0.3 to −0.1] percentage points). Among both the treatment groups, there were no significant changes observed in FBG from baseline to week 26 (ETD, 0 [95% CI, −6 to 5] mg/dL; $P = 0.90$), mean weekly insulin dose during the last 2 weeks of treatment, or body weight change from baseline to week 26 (2.8 kg versus 2.3 kg; ETD, 0.46 [95% CI, −0.19 to 1.10] kg; $P = 0.17$). The rates of hypoglycemia were higher in the icodec group than in the insulin degludec group. Thus, it was concluded that insulin icodec, when compared to insulin degludec, was noninferior ($P < 0.001$) and superior ($P = 0.002$) in terms of HbA1c reduction; however, it demonstrated a significantly higher rate of hypoglycemia in insulin naïve T2D subjects. [18]

A randomized, open-label, multicentre, treat-to-target, non-inferiority, phase 3a trial, performed at 80 sites involving adults (≥18 years of age), was done to assess the efficacy and safety of once-weekly icodec in comparison to once-daily insulin glargine U100 (glargine U100) in individuals with T2D on a basal-bolus regimen. This was done over a 26-week period, and 582 subjects were randomly assigned (1:1) to receive once-weekly icodec or once-daily glargine U100 as a basal dose along with 2 - 4 daily bolus insulin aspart injections. The primary outcome

was to observe the change in HbA1c from baseline to week 26. Towards the end of the 26-week period, it was observed that the mean change in values of HbA1c level was −1.16 percentage points (baseline 8.29%) and -1.18 percentage points in the icodec and glargine U100 group (baseline 8.31%), respectively. There were no significant differences between the groups in terms of adverse events or hypoglycemia rates. This showed that insulin icodec was non-inferior compared to glargine U100 (estimated treatment difference 0.02 percentage points [95% CI −0.11 to 0.15], $p < 0.0001$). [19]

A 52-week, randomized, open-label, parallel-group, phase 3a trial with real-world elements was performed in 176 sites to compare the effectiveness and safety of insulin icodec compared to insulin glargine U100, or insulin glargine U300 when titrated with a dosing guide app (icodec with app) dosed as per standard practice. 1085 adults (≥18 years of age) patients with T2D and who were insulin naïve were recruited for the study. The primary outcome was to observe the change in HbA1c from baseline to week 52, and secondary outcomes were patient-reported outcomes (Treatment Related Impact Measure for Diabetes [TRIM-D] compliance domain score and change in Diabetes Treatment Satisfaction Questionnaire [DTSQ] total treatment satisfaction score). At the end of 52 weeks, insulin icodec demonstrated noninferiority ($P < 0.001$) and superiority ($P = 0.009$) with respect to the estimated mean change in HbA1c from baseline to week 52. Additionally, patient-reported outcomes were also seen to be more favorable with icodec with an app than with the glargine analogues. There were no significant differences between the groups in terms of adverse events or hypoglycemia rates. [20]

A 52-week randomized, open-label, treat-to-target, phase 3a trial was done at 99 sites, in adults (≥18 years of age) patients with T1D to assess the efficacy and safety of once-weekly subcutaneous insulin icodec and once-daily insulin degludec. 582 subjects were randomly assigned (1:1) to once-weekly icodec or once-daily degludec, along with insulin aspart (≥2 daily injections). The primary endpoint was the change in HbA1c from baseline to week 26, tested for non-inferiority. Towards the end of 26 weeks, the estimated mean changes in HbA1c were −0.47 percentage points and −0.51 percentage points, from baseline values of 7.59% (icodec) and 7.63% (degludec), respectively (estimated treatment difference 0.05 percentage points [95% CI −0.13 to 0.23]). Thus, the non-inferiority of icodec is shown in comparison to degludec ($p = 0.0065$). The combined rates of clinically significant or severe hypoglycemia (baseline to week 26) were statistically significantly higher with icodec than degludec (19.9 versus 10.4 events per patient-year of exposure; estimated rate ratio 1.9 [95% CI 1.5 to 2.3]; $p < 0.0001$). Therefore, in adult T1D individuals, although the risk of hypoglycemic events remains higher with insulin icodec, it has been shown to be noninferior to insulin degludec. [21]

In a meta-analysis comparing once-weekly insulin analogues, namely insulin icodec and basal insulin Fc (BIF), in T2D individuals, it was seen that the former led to improved glycemic control compared to the latter. Although both shared similar safety profiles, a larger number of studies with icodec favor its use more

than once daily in basal insulin formulations like degludec or glargine (U100 or U300). [22]

Table 1. Summary of ongoing trials for once weekly insulin icodec.

	ONWARDS 1 Icodec vs. Glargine U100 in T2DM Insulin-Naïve	**ONWARDS 2** Icodec vs. Degludec U100 in T2DM in Basal Bolus	**ONWARDS 3** Icodec vs. Degludec in T2DM Insulin-Naïve	**ONWARDS 4** Icodec vs. Glargine U100 in T2DM in Basal Bolus	**ONWARDS 5** Icodec vs. Once-Daily Insulin in T2DM Insulin-Naïve with Dosing Guide App	**ONWARDS 6** Icodec vs. Degludec in T1DM
Number of patients	984	526	588	582	1085	582
Time frame	78 weeks	26 weeks	26 weeks	26 weeks	52 weeks	52 weeks
Primary End-point	HbA1c reduction at 52 weeks	HbA1c reduction at 26 weeks	HbA1c reduction at 26 weeks	HbA1c reduction at 26 weeks	HbA1c reduction at 52 weeks	HbA1c reduction at 26 weeks
Observations	Once-weekly insulin icodec demonstrated a better glycemic control than once-daily insulin glargine U100 in insulin naïve T2D adults	Once-weekly icodec was non-inferior and superior to once-daily degludec as shown in HbA1c reduction after 26 weeks, in spite of the associated mild weight gain	Once-weekly insulin icodec when compared to insulin degludec was noninferior and superior in terms of HbA1c reduction. However, icodec had a significantly higher rate of hypoglycemia in insulin naïve T2D subjects.	Once-weekly insulin icodec was non-inferior compared to glargine U100	Once-weekly insulin icodec demonstrated noninferiority and superiority with respect to the estimated mean change in HbA1c from baseline to week 52.	Once-weekly insulin icodec in T1D individuals, the risk of hypoglycemic events remains higher; it has been shown to be noninferior to insulin degludec.

7. Conclusion

While the main issue with insulin therapy involves multiple dosing, it is also one of the main contributors to poor adherence to therapy, thereby causing an increase in poor patient outcomes and healthcare costs. Hence, once weekly basal insulin formulations offer to be the solution to this predicament by decreasing the frequency of insulin dosing in both T1D and T2D individuals who require insulin treatment (Table 1). However, more real-world studies are warranted to look at the usefulness of these neo-ultra basal insulins and their risks of hypoglycemia in specific populations like children, pregnancy and the elderly.

Author Contribution

Conception and design: Dr. Jimmy J Thomas; acquisition, analysis, or interpretation of data: Dr. Jimmy J Thomas; drafting the work or revising: Dr. Nidhi Mathews; final approval of the manuscript: Dr. Jimmy J Thomas, Dr. Nidhi Mathews.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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